BCU | 2015 VOL 14 | ISSUE 2

# Breast Cancer® UPDATE

## Conversations with Oncology Investigators

### Bridging the Gap between Research and Patient Care

**FACULTY INTERVIEWS**

Beth Overmoyer, MD
Sandra M Swain, MD
Joyce O'Shaughnessy, MD
Ruth M O'Regan, MD

**EDITOR**

Neil Love, MD

**CONTENTS**

2 Audio CDs
Monograph

CME Certified

# *Breast Cancer Update*

## A Continuing Medical Education Audio Series

### OVERVIEW OF ACTIVITY

Breast cancer (BC) 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 an evidence-based algorithm for the treatment of hormone-sensitive advanced BC, including the use of endocrine, chemotherapeutic and biologic agents.
- Implement a long-term clinical plan for the management of metastatic HER2-positive BC, incorporating existing, recently approved and investigational targeted treatments.
- Evaluate available and emerging data guiding the use of genomic assays to optimize decision-making regarding adjuvant chemotherapy and extended endocrine therapy.
- Appraise novel treatment strategies under investigation in advanced BC (eg, anti-PD-1/PD-L1 antibodies, androgen receptor inhibitors).
- Apply the results of current clinical data to the management of triple-negative BC.
- Develop a plan of care for patients with advanced inflammatory BC, incorporating existing and novel treatment approaches.

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Release date: January 2016; Expiration date: January 2017

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## EDITOR

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INTERVIEW

## Beth Overmoyer, MD

Dr Overmoyer is Assistant Professor of Medicine at Harvard Medical School and Director of the Inflammatory Breast Cancer Program and Medical Oncologist in the Susan F Smith Center for Women's Cancers Breast Oncology Program at Dana-Farber Cancer Institute in Boston, Massachusetts.

### Tracks 1-15

Track 1 **Case discussion:** A 40-year-old woman presents with breast enlargement, nipple inversion and slight erythema and is diagnosed with ER/PR-negative, HER2-positive inflammatory breast cancer (IBC)

Track 2 Treatment of HER2-positive IBC

Track 3 Biology of HER2-positive IBC

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## Select Excerpts from the Interview

### Tracks 2-4, 6-7

**DR LOVE:** Would you discuss the management of HER2-positive inflammatory breast cancer (IBC)?

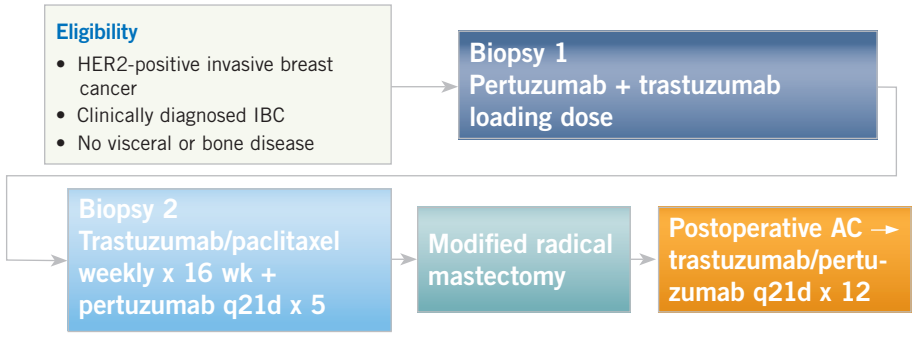
**DR OVERMOYER:** About 30% to 40% of patients with IBC have HER2-positive tumors. These patients most often have ER/PR-negative disease and are typically exquisitely sensitive to HER2-targeted therapy. We now have a study under way in which patients undergo a biopsy and then receive a preoperative loading dose of pertuzumab and trastuzumab (1.1). Then they have another biopsy, start weekly trastuzumab/paclitaxel and continue with that combination and add pertuzumab every 3 weeks to complete 16 doses before surgery. The primary endpoint is pathologic complete response (pCR) rate, and we're opening the study to other institutions now.

We're trying to minimize chemotherapy and maximize HER2-directed therapy in this population. How much chemotherapy patients with HER2-positive disease need

**1.1**

**Phase II Trial of Paclitaxel/Trastuzumab/Pertuzumab as Preoperative Therapy for HER2-Positive Inflammatory Breast Cancer (IBC)**

**Protocol ID:** NCT01796197 **Target Accrual:** 30




**www.clinicaltrials.gov**. Accessed December 2015.

is unclear, but we have seen clinically that these individuals experience dramatic responses with only pertuzumab and trastuzumab.

**DR LOVE:** What interesting novel regimens and/or concepts are being investigated for patients with triple-negative IBC or ER-positive, HER2-negative IBC?

**DR OVERMOYER:** Some retrospective studies have shown that 40% to 50% of IBC is triple-negative. Unfortunately for these patients, outcomes are poor. Interestingly, nearly 100% of our patients with triple-negative IBC exhibit overexpression of STAT3, and thus we are evaluating agents that target the JAK2/STAT3 pathway.

We are initiating a Phase II study evaluating the JAK1/2 inhibitor ruxolitinib with paclitaxel followed by dose-dense AC as preoperative therapy for triple-negative IBC (NCT02041429). We also recently closed a Phase I study at our institution evaluating ruxolitinib/paclitaxel until response then ruxolitinib alone for patients with metastatic breast cancer (mBC). Several individuals on that trial had IBC, and one who initially presented with metastatic triple-negative IBC is still on the study. She has been receiving single-agent ruxolitinib for about a year and has no evidence of disease. So some disease subtypes clearly respond to this agent.

To answer the second part of your question, 20% to 40% of patients with IBC have ER/PR-positive, HER2-negative disease. We're planning a trial evaluating eribulin because in preclinical mouse models, targeting angiogenesis can change the vascular flow and change EMT (epithelial-to-mesenchymal transition)-directed genes. Our study is trying to mimic that by using eribulin followed by dose-dense AC.

We also have a study of eribulin in the first- and second-line settings for metastatic disease. I've administered first-line eribulin to many patients, and it's well tolerated. The major toxicity is neuropathy, which can be severe. You can work around the neutropenia using growth factors. Alopecia occurs more than I'd like to say, but eribulin is more favorable than paclitaxel in this regard, and patients can receive therapy for a considerable amount of time before we see significant hair loss.

Another study is evaluating eribulin in 2 cohorts of patients with mBC, those with triple-negative breast cancer (TNBC) and those with ER-positive disease (NCT01827787).

## Tracks 12-14

**DR LOVE:** What is your experience with the CDK4/6 inhibitors palbociclib and abemaciclib for patients with ER-positive mBC?

**DR OVERMOYER:** Palbociclib in combination with letrozole for up-front therapy doubles progression-free survival (PFS) from about 10 to 20 months (Finn 2015), and the PALOMA-3 data indicate that this agent is active when administered with fulvestrant to patients with disease progression after hormone therapy (Turner 2015a; [1.2]). We would expect it also to enhance therapy in TNBC, so we're evaluating it with chemotherapy in that setting.

**DR LOVE:** The situation people ask us about most is that of relapse during adjuvant hormone therapy, particularly aromatase inhibitors (AIs). How do you evaluate those patients? Do they all receive palbociclib, or do some receive hormone therapy alone?

**DR OVERMOYER:** In newly relapsed or first- or second-line recurrent disease after a patient's exposure to hormone therapy, I try to administer palbociclib in addition to the AI. If they've already received an AI, I use fulvestrant and palbociclib. I haven't had much pushback from insurance companies, so for patients who develop relapse on an adjuvant AI fulvestrant and palbociclib would be my off-study choice.

With regard to abemaciclib, one study suggested a response rate of approximately 30% with that drug as monotherapy in ER-positive disease before chemotherapy, although in terms of toxicity neutrophil counts are a problem (Tolaney 2014; [1.3]). We routinely reduce the dose due to neutropenia.

Abemaciclib is also being evaluated in combination with hormonal therapy. We have a study under way at our institution using abemaciclib and anastrozole. I recently

**1.2**

**PALOMA-3: Results of a Phase III Study of Palbociclib with Fulvestrant versus Fulvestrant Alone in ER-Positive, HER2-Negative Advanced Breast Cancer After Failure of Endocrine Therapy**

| Efficacy | Fulvestrant + palbociclib (n = 347) | Fulvestrant + placebo (n = 174) | Hazard ratio | *p*-value |
|---|---|---|---|---|
| Overall response rate | 10.4% | 6.3% | NR | 0.16 |
| Median PFS | 9.2 mo | 3.8 mo | 0.422 | <0.001 |

At interim analysis, overall survival data were immature, with a total of 28 deaths: Fulvestrant/palbociclib (n = 19), fulvestrant/placebo (n = 9).

| | Fulvestrant + palbociclib (n = 345) | | Fulvestrant + placebo (n = 172) | |
|---|---|---|---|---|
| Select adverse events | All grades | Grade 3 or 4 | All grades | Grade 3 or 4 |
| Neutropenia | 79% | 62% | 3.5% | 0.6% |
| Fatigue | 38% | 2% | 26.7% | 1.2% |
| Nausea | 29% | 0% | 26.2% | 0.6% |
| Alopecia | 14.8% | 0% | 5.8% | 0% |

NR = not reported; PFS = progression-free survival

Turner NC et al. *N Engl J Med* 2015a;373(3):209-19; Turner NC et al. *Proc ASCO* 2015b;**Abstract LBA502**.

**1.3**

## Efficacy and Safety of Abemaciclib (LY2835219) Monotherapy for Patients with Metastatic Breast Cancer

| Efficacy | All patients (N = 47) | HR-positive (N = 36) |
|---|---|---|
| **Objective response rate** (CR + PR) | 12 (25.5%) | 12 (33.3%) |
| **Clinical benefit rate** (CR + PR + SD ≥24 wk) | 23 (48.9%) | 22 (61.1%) |
| **Disease control rate** (CR + PR + SD) | 33 (70.2%) | 29 (80.6%) |
| **Select adverse events** (N = 47) | **Grade 3 or 4** | **All grades** |
| Diarrhea | 4 (8.5%) | 32 (68.1%) |
| Nausea | 2 (4.3%) | 28 (59.6%) |
| Fatigue | 1 (2.1%) | 21 (44.7%) |
| Vomiting | 1 (2.1%) | 21 (44.7%) |
| Decreased neutrophil count | 10 (21.2%) | 19 (40.4%) |
| Decreased platelet count | 5 (10.6%) | 15 (31.9%) |

CR = complete response; PR = partial response; SD = stable disease

Tolaney S et al. San Antonio Breast Cancer Symposium 2014;**Abstract P5-19-13**.

placed a 70-year-old woman on this trial. She presented with ER/PR-positive, HER2-negative locally advanced disease with involvement of the ovaries and bone, and although initially we had to hold therapy and then reduce the dose because of diarrhea, she has now been receiving this combination for a year and is faring beautifully.

**DR LOVE:** Where does everolimus fit in?

**DR OVERMOYER:** Because everolimus is approved with exemestane as second-line therapy, I use an AI and palbociclib followed by exemestane and everolimus. Some of my colleagues' experiences with everolimus have been more favorable than mine, however. My patients have had a hard time with mucositis and fatigue, and I have dose reduced every time I've used it. It's difficult to keep patients on therapy. The maximum duration I've administered was 6 months, and then I had to stop the everolimus and continue the exemestane alone. ■

## SELECT PUBLICATIONS


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

Finn RS et al. **The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study.** *Lancet Oncol* 2015;16(1):25-35.

Tolaney SM et al. **Clinical activity of abemaciclib, an oral cell cycle inhibitor, in metastatic breast cancer.** San Antonio Breast Cancer Symposium 2014;**Abstract P5-19-13**.

Turner NC et al. **Palbociclib in hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2015a;373(3):209-19.

Turner NC et al. **PALOMA3: A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy.** *Proc ASCO* 2015b;**Abstract LBA502**.

INTERVIEW

## Sandra M Swain, MD

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

### Tracks 1-13

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**Track 2** Therapeutic options for patients with HER2-positive disease who experience early relapse after adjuvant treatment with chemotherapy and trastuzumab

**Track 3** MARIANNE: Results of a Phase III study of T-DM1 with or without pertuzumab versus trastuzumab and a taxane as first-line therapy for HER2-positive mBC

**Track 4** Incorporation of pertuzumab into the treatment algorithm for mBC

**Track 5** Perspective on the ongoing Phase III APHINITY trial and the role of pertuzumab in the adjuvant setting

**Track 6** Safety profile of pertuzumab

**Track 7** Tolerability of T-DM1 and efficacy in treating brain metastases

**Track 8** APT: Results of a Phase II trial of adjuvant paclitaxel/trastuzumab for HER2-positive, node-negative BC

**Track 9** Primary analysis of the Phase III ExteNET study: Neratinib after adjuvant chemotherapy with trastuzumab for HER2-positive early BC

**Track 10** Choice of endocrine therapy for patients with ER-positive ductal carcinoma in situ

**Track 11** Use of the Breast Cancer Index℠ to predict risk of recurrence and benefit of extended adjuvant endocrine therapy

**Track 12** Clinical utility of the Onco*type* DX® assay in early-stage BC

**Track 13** Perspective on the use of next-generation sequencing for patients with BC

## Select Excerpts from the Interview

### Tracks 1-4, 6-7

**DR LOVE:** The final overall survival results of the CLEOPATRA trial for patients with HER2-positive mBC were recently published (Swain 2015). Would you discuss the rationale for and results of the study, for which you were one of the lead investigators?

**DR SWAIN:** CLEOPATRA was a Phase III trial that evaluated the addition of pertuzumab to trastuzumab and docetaxel as first-line therapy. Previous data demonstrated synergy with trastuzumab and taxanes. Docetaxel was chosen as chemotherapy because it was a worldwide study. We experienced a lot of difficulty with accrual in the United States because of the docetaxel backbone, which is usually not administered in metastatic disease. Eventually, we were able to accrue more than 800 patients, with only 16% of them in the United States.

I was surprised at how impressive the results were, with a 6-month PFS benefit (Baselga 2012). The median overall survival was 56.5 months on the pertuzumab arm versus approximately 41 months on the control arm, which is incredible (Swain 2015). What I see from my experience and hear from colleagues is that the response rates are fantastic. So the results are holding up in practice also.

**DR LOVE:** How do you approach a patient who experiences early relapse after receiving a taxane and trastuzumab in your practice outside a trial setting?

**DR SWAIN:** I would offer pertuzumab and trastuzumab with vinorelbine, which is an active regimen. T-DM1 may also be reasonable but may not elicit a response in these patients. I believe for patients with disease that is resistant to trastuzumab, other agents should be considered.

**DR LOVE:** What does pertuzumab add in terms of toxicity?

**DR SWAIN:** Diarrhea occurs in approximately 60% of patients, and Grade 3 or 4 diarrhea, which can lead to dehydration, is observed in about 10% of patients. Dermatologic toxicity occurs in 25% of patients, but I haven't observed many cases. Rash can occur frequently with docetaxel, but the incidence is higher in patients who also receive pertuzumab. The incidence of febrile neutropenia is increased with pertuzumab, especially in the Asian population, in whom it occurs approximately 25% of the time.

**DR LOVE:** MARIANNE was a Phase III trial that evaluated T-DM1 with or without pertuzumab versus trastuzumab and a taxane for the first-line treatment of HER2-positive mBC. Would you talk about the design and results of the study?

**DR SWAIN:** This trial was designed before the CLEOPATRA data were presented, but considering those results in hindsight, it would have been better for pertuzumab to be added to the control arm of trastuzumab with a taxane. The findings were disappointing, with no difference between the arms. T-DM1 with pertuzumab was noninferior to T-DM1 alone or to trastuzumab/taxane, but it certainly wasn't superior as we had hoped it would be (Ellis 2015; [2.1]).

**DR LOVE:** What's your experience with T-DM1 in terms of the tolerability?

**DR SWAIN:** T-DM1 is well tolerated in most patients, the major toxicity being elevated liver enzymes and a decrease in platelets. These side effects may require dose reductions. I had a patient who was unable to tolerate lapatinib/capecitabine but experienced an unbelievable response to T-DM1. So in many patients it works well because the quality of life is good with low toxicity.

## Track 8

**DR LOVE:** What are your thoughts on the APT trial investigating adjuvant paclitaxel and trastuzumab for HER2-positive breast cancer?

**DR SWAIN:** Trastuzumab is known to be effective in the adjuvant setting, but many patients don't need intensive chemotherapy. So the Dana-Farber group conducted a trial in which patients with small, node-negative, HER2-positive tumors received adjuvant paclitaxel in combination with trastuzumab. The results were outstanding. The 3-year rate of disease-free survival was 99% for patients with ER-negative tumors and approximately 98% for those with ER-positive ones (Tolaney 2015). So I believe that adjuvant paclitaxel and trastuzumab is an option for some patients.

**2.1**

### MARIANNE: Results of a Phase III Study of T-DM1 with or without Pertuzumab versus Trastuzumab with a Taxane as First-Line Therapy for HER2-Positive Metastatic Breast Cancer

| Efficacy | HT (n = 365) | T-DM1 (n = 367) | T-DM1 + P (n = 363) |
|---|---|---|---|
| Median progression-free survival | 13.7 mo | 14.1 mo | 15.2 mo |
| Stratified HR versus HT | — | 0.91 | 0.87 |
| Overall response rate | 67.9% | 59.7% | 64.2% |
| Median duration of response | 12.5 mo | 20.7 mo | 21.2 mo |
| **Select adverse events** | **HT (n = 353)** | **T-DM1 (n = 361)** | **T-DM1 + P (n = 366)** |
| Alopecia | 59.8% | 6.6% | 9.0% |
| Diarrhea | 48.7% | 25.2% | 48.1% |
| Peripheral neuropathy | 28.0% | 13.3% | 17.8% |
| Neutropenia | 22.7% | 11.4% | 8.7% |

HT = trastuzumab/taxane; P = pertuzumab

Median overall survival was not yet reached for any arm.

Ellis P et al. *Proc ASCO* 2015;**Abstract 507**.

As a follow-up to that study, the ATEMPT trial is evaluating T-DM1 versus paclitaxel and trastuzumab for Stage I, HER2-positive breast cancer. I believe it's a great study. Some patients with limited disease don't need the aggressive chemotherapy that we administer. At ASCO 2015, Nadia Harbeck presented a trial that assessed 12 weeks of neoadjuvant T-DM1 with or without endocrine therapy for hormone receptor–positive, HER2-positive early breast cancer. They reported high pCR rates (Harbeck 2015; [2.2]). So those data support the concept of using T-DM1 for patients with a lower risk of recurrence in the adjuvant setting.

**2.2**

### ADAPT: Results of a Phase II Trial of Neoadjuvant T-DM1 with or without Endocrine Therapy (ET) in ER-Positive, HER2-Positive Early Breast Cancer

| | T-DM1 (n = 37) | T-DM1 + ET (n = 48) | Trastuzumab + ET (n = 45) |
|---|---|---|---|
| **Efficacy** | | | |
| Pathologic complete response | 40.5% | 45.8% | 6.7% |
| **Select AEs (any grade)** | **T-DM1 (n = 37)** | **T-DM1 + ET (n = 48)** | **Trastuzumab + ET (n = 45)** |
| AST increase | 19% | 10% | 0% |
| ALT increase | 22% | 6% | 2% |
| Hepatotoxicity | 3% | 4% | 0% |
| Thrombocytopenia | 30% | 15% | 4% |

AEs = adverse events

Harbeck N et al. *Proc ASCO* 2015;**Abstract 506**.

## Tracks 11-13

**DR LOVE:** What are your thoughts on the ability of the Breast Cancer Index assay to predict the risk of recurrence up front and after 5 years of adjuvant endocrine therapy, and do you use it in practice?

**DR SWAIN:** The data with the Breast Cancer Index and its ability to predict the risk of distant recurrence appear to be good (Sgroi 2013). I have recently started using the assay to determine whether to continue endocrine therapy beyond 5 years. Some patients have small, low-risk disease with negative nodes and a low Onco*type* DX Recurrence Score. In those patients it is beneficial to attempt to determine whether continuing hormonal therapy for 10 years makes sense.

**DR LOVE:** Do you use the Onco*type* DX assay for decision-making in the front-line setting?

**DR SWAIN:** I order it for patients who have node-negative disease and for some with node-positive disease. I recently had a patient with a small ER-positive, PR-negative, node-negative tumor and an intermediate Onco*type* DX Recurrence Score of 25.

Tumors that are luminal B subtype and ER-positive, PR-negative may respond better to chemotherapy. So I recommended chemotherapy for this patient. If patients have node-negative disease, I generally administer docetaxel/cyclophosphamide.

**DR LOVE:** Would you comment on the use of next-generation sequencing for patients with breast cancer?

**DR SWAIN:** I believe we are at the tip of the iceberg in terms of using next-generation sequencing. Eventually we will be doing it for all patients. Currently in our group we're developing a consensus on which patients we should order it for. One example would be patients who have metaplastic breast cancer who don't experience a response to chemotherapy. I've ordered it in the adjuvant setting for a patient who had many positive nodes. It indicated that an mTOR inhibitor might be beneficial, which pointed to the adjuvant everolimus trial. It may be especially useful for patients who are experiencing relapse.

I would like to see us ordering next-generation sequencing for all patients. It is expensive, but we can learn something about the different mutations. Even though they may not be "actionable" now, this information will be helpful to us in the future. ■

### SELECT PUBLICATIONS


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

Sgroi D et al. **Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population.** *Lancet Oncol* 2013;14(11):1067-76.

Swain SM et al; CLEOPATRA Study Group. **Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer.** *N Engl J Med* 2015;372(8):724-34.

Tolaney S et al. **Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.** *N Engl J Med* 2015;372(2):134-41.

Tolaney S et al. **A Phase II study of adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.** San Antonio Breast Cancer Symposium 2013;**Abstract S1-04**.

INTERVIEW

## Joyce O'Shaughnessy, MD

Dr O'Shaughnessy is Chair of the Breast Cancer Research Program at Baylor Charles A Sammons Cancer Center in Dallas, Texas.

### Tracks 1-11

| | |
|---|---|
| Track 1 | Efficacy of androgen receptor antagonists in metastatic triple-negative breast cancer (mTNBC) |
| Track 2 | **Case discussion:** A 45-year-old woman with TNBC and blastic bone metastases whose disease progresses after first-line chemotherapy experiences disease stabilization after receiving enzalutamide on a clinical trial |
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| Track 9 | GeparSepto GBG 69: Results of a Phase III trial evaluating *nab* paclitaxel versus solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early BC |
| Track 10 | Activity of eribulin as first-line therapy for patients with mBC |
| Track 11 | **Case discussion:** A 50-year-old woman with heavily pretreated ER-positive/HER2-positive PIK3CA-mutant mBC achieves an excellent response to eribulin and trastuzumab |

## Select Excerpts from the Interview

### Track 1

**DR LOVE:** What is the role of androgen receptor (AR) antagonists in the management of mTNBC?

**DR O'SHAUGHNESSY:** Targeting AR in mTNBC is an important strategy. Recently, we saw the effects of a powerful pure AR antagonist, enzalutamide, in mTNBC. As a single agent, enzalutamide elicited an impressive clinical benefit rate of 39% at 16 weeks in patients with advanced AR-positive TNBC (Traina 2015; [3.1]).

I was interested in the results of the enzalutamide study because the investigators had access to the "PREDICT AR" gene expression assay. The PREDICT AR assay enables us to take patients with AR-positive TNBC and ask, "Which individuals have AR as a driving transcription factor in their disease?" The assay seems to be better than measuring AR by IHC testing for staining greater than 10%. Most patients with PREDICT AR-positive disease tend to have higher expression of AR. However, some

**3.1**

**MDV3100-11: Efficacy and Safety Results of a Phase II Trial of Enzalutamide for Patients with Advanced Androgen Receptor (AR)-Positive, Triple-Negative Breast Cancer**

| | | Intention-to-treat (ITT) population according to PREDICT AR status* | |
|---|---|---|---|
| **Efficacy** | **Evaluable patients** (n = 75) | **AR-positive** (n = 56) | **AR-negative** (n = 62) |
| CR/PR | 8% | 9% | 3% |
| CBR at 16 weeks | 35% | 39% | 11% |
| CBR at 24 weeks | 29% | 36% | 6% |
| Median PFS | 14.7 weeks | 16.1 weeks | 8.1 weeks |
| Median OS | NR | NYR | 32.1 weeks |
| **TRAEs in ITT** (n = 118) | **All grades** | **Grade ≥3** | |
| Fatigue | 34% | 5% | |
| Nausea | 25% | 0% | |
| Constipation | 8% | 1% | |
| Back pain | 2% | 1% | |
| Dyspnea | 4% | 1% | |

CR = complete response; PR = partial response; CBR = clinical benefit rate; PFS = progression-free survival; OS = overall survival; NR = not reported; NYR = not yet reached; TRAEs = treatment-related adverse events

* PREDICT AR is a genomic signature associated with androgen biology to predict response to enzalutamide in triple-negative breast cancer.

**Safety data were consistent with the known profile of enzalutamide.**

Traina TA et al. *Proc ASCO* 2015;**Abstract 1003**.

patients with disease categorized as PREDICT AR-positive express lower levels of AR by immunohistochemistry.

Once we have more data about patients who would benefit most from enzalutamide, we must conduct clinical trials in early metastatic disease and for patients at high risk in the adjuvant setting. This will include patients with TNBC and the 50% of patients with ER-negative, HER2-positive, AR-positive breast cancer.

## Track 4

**DR LOVE:** Would you discuss your perspective on the results of the trials evaluating the safety and efficacy of immune checkpoint inhibitors in TNBC?

**DR O'SHAUGHNESSY:** In the Phase Ib KEYNOTE-012 trial of pembrolizumab, an anti-PD-1 antibody, in patients with advanced TNBC, an overall response rate of approximately 19% was reported (Nanda 2014). Some of the responses were unquestionably more durable than we would ever see with chemotherapy in heavily pretreated disease. Pembrolizumab has excellent tolerability. The safety issues in terms of serious pneumonitis and colitis are not as apparent as they are with ipilimumab. Both pembrolizumab and the anti-PD-L1 antibody atezolizumab (MPDL3280A) (Emens 2014) appear active in trials focusing on patients with PD-L1-positive mTNBC.

I believe we need a better handle on the subset of patients who will benefit most from these agents. The Phase II KEYNOTE-086 trial of pembrolizumab monotherapy for patients with mTNBC is currently ongoing (NCT02447003). I am excited about this trial because all patients with mTNBC will be able to receive this agent. It includes a cohort of patients with PD-L1-negative disease and another with PD-L1-positive TNBC. It will be a large trial, and lots of data will be collected in terms of which patients have the potential for substantial benefit from treatment.

## Tracks 8-10

**DR LOVE:** The recently published results of the Phase III CALGB-40502 trial for patients with chemotherapy-naïve advanced breast cancer demonstrated that weekly nanoparticle albumin-bound (*nab*) paclitaxel was not superior to weekly solvent-based paclitaxel (Rugo 2015). What are your thoughts on administering *nab* paclitaxel in this population of patients in your practice?

**DR O'SHAUGHNESSY:** I predominantly administer weekly *nab* paclitaxel as a toxicity reduction strategy to avoid chronic steroid use with regular paclitaxel, which causes extreme fatigue for patients over time. We have preclinical data and ongoing clinical trials that are evaluating glucocorticoid receptor (GR) blockade. Also, it has been shown that steroids signal through GR in TNBC and that this leads to drug resistance. An ongoing Phase I trial is evaluating mifepristone, a GR antagonist, and eribulin in mTNBC (NCT02014337).

We conducted a large Phase II trial in later-line mBC in which we evaluated weekly *nab* paclitaxel at 100 or 125 mg/m$^2$ on a 3-week-on, 1-week-off schedule. In our experience, only 8% of patients experienced Grade 3 peripheral neuropathy at 100 mg/m$^2$ (Blum 2007) compared to 24% Grade 3 peripheral neuropathy with weekly paclitaxel at 80 mg/m$^2$ observed in the earlier-line setting. On this basis, I believe I get more mileage using weekly *nab* paclitaxel with less peripheral neuropathy.

**DR LOVE:** What is your perspective on the results of the Phase III GeparSepto trial comparing *nab* paclitaxel to solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (Untch 2014)?

**DR O'SHAUGHNESSY:** The results are interesting and encouraging, indicating that the pCR rate is significantly higher with *nab* paclitaxel (38%) versus solvent-based paclitaxel (29%) when administered on a weekly basis before anthracycline-based chemotherapy. I would like to see an accelerated approval of *nab* paclitaxel in this setting based on the pCR rates.

**DR LOVE:** Can you comment on the role of eribulin for patients with HER2-positive advanced breast cancer?

**DR O'SHAUGHNESSY:** As first-line therapy in HER2-positive advanced breast cancer, eribulin in combination with trastuzumab produced a respectable objective response rate of 71.2% in a Phase II trial. The median PFS overall was 11.6 months. These patients experienced more Grade 3 or higher neuropathy than is normally observed in later-line therapy because they received eribulin for a long time (Wilks 2014; [3.2]). Eribulin is a highly active agent. It rivals any of the other strategies for first-line metastatic disease. It is another agent that can be safely and effectively combined with trastuzumab. The results of this study have given me the license to use it in later-line HER2-positive metastatic disease.

**3.2**

## Efficacy and Safety of Eribulin in Combination with Trastuzumab as First-Line Therapy for HER2-Positive Locally Recurrent or Metastatic Breast Cancer

| Response | Eribulin/trastuzumab (n = 52) | |
|---|---|---|
| Objective response rate | 37 (71.2%) | |
| Complete response | 3 (5.8%) | |
| Partial response | 34 (65.4%) | |
| Median DoR | 11.1 months | |
| **Median PFS** | | |
| All patients (n = 52) | 11.6 months | |
| ER-positive (n = 35) | 13.1 months | |
| ER/PR-negative (n = 15) | 9.5 months | |
| **Adverse events** (n = 52) | **All grades** | **Grade ≥3** |
| Fatigue | 36 (69.2%) | 4 (7.7%) |
| Peripheral neuropathy | 36 (69.2%) | 14 (26.9%) |
| Neutropenia | 31 (59.6%) | 20 (38.5%) |
| Febrile neutropenia | 4 (7.7%) | 4 (7.7%) |

DoR = duration of response; PFS = progression-free survival

Wilks S et al. *Clin Breast Cancer* 2014;14(6):405-12.

A Phase II study of eribulin for patients with advanced HER2-negative breast cancer demonstrated a response rate of approximately 30% and a median PFS of approximately 7 months (McIntyre 2014). An ongoing Phase III trial is comparing eribulin to standard weekly paclitaxel as first- or second-line therapy for HER2-negative locally recurrent or metastatic breast cancer (NCT02037529). This will provide data on whether eribulin is an agent that will have benefit compared to weekly standard-formulation paclitaxel in HER2-negative advanced disease. ■

## SELECT PUBLICATIONS


Blum J et al. **Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes.** *Clin Breast Cancer* 2007;7(11):850-6.

Emens LA et al. **Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer.** San Antonio Breast Cancer Symposium 2014;**Abstract PD1-6**.

McIntyre K et al. **Phase 2 study of eribulin mesylate as first-line therapy for locally recurrent or metastatic human epidermal growth factor receptor 2-negative breast cancer.** *Breast Cancer Res Treat* 2014;146(2):321-8.

Nanda R et al. **A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer.** San Antonio Breast Cancer Symposium 2014;**Abstract S1-09**.

Rugo HS et al. **Randomized phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound *nab*-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance).** *J Clin Oncol* 2015;33(21):2361-9.

Untch M et al. **A randomized phase III trial comparing neoadjuvant chemotherapy with weekly nanoparticle-based paclitaxel with solvent-based paclitaxel followed by anthracyline/cyclophosphamide for patients with early breast cancer (GeparSepto); GBG 69.** San Antonio Breast Cancer Symposium 2014;**Abstract PD2-6**.

INTERVIEW

## Ruth M O'Regan, MD

Dr O'Regan is Professor of Medicine and Chief of the Division of Hematology/Oncology at the University of Wisconsin Carbone Cancer Center in Madison, Wisconsin.

### Tracks 1-10

| | |
|---|---|
| Track 1 | **Case discussion:** A 55-year-old woman with ER/PR-positive, HER2-negative Stage I BC and an Onco*type* DX RS of 17 who declines chemotherapy and receives tamoxifen followed by anastrozole |
| Track 2 | Prognostic and predictive utility of the Breast Cancer Index for ER-positive BC |
| Track 3 | Evaluation of the Breast Cancer Index in patients with ER-positive, HER2-positive BC for risk of late recurrence and potential benefit of extended endocrine therapy |
| Track 4 | **Case discussion:** A 40-year-old woman with ER/PR-positive, HER2-negative BC and de novo metastatic disease to the bones and liver |
| Track 5 | Effect of primary tumor resection on outcomes for patients with mBC |
| Track 6 | Efficacy of the CDK4/6 inhibitor palbociclib with letrozole as first-line therapy or with fulvestrant as second-line therapy for ER-positive, HER2-negative mBC |
| Track 7 | Incorporation of palbociclib and everolimus into the treatment algorithm for patients with ER-positive mBC |
| Track 8 | Clinical trials with palbociclib or everolimus combined with adjuvant endocrine therapy |
| Track 9 | Discordant expression of hormone receptors in primary and metastatic tumors |
| Track 10 | Activity and tolerability of the novel agents abemaciclib and ribociclib for ER-positive mBC |

## Select Excerpts from the Interview

### Tracks 1-3

**DR LOVE:** Could you discuss how you integrate the 21-gene Recurrence Score for patients with breast cancer in your practice?

**DR O'REGAN:** I use the Onco*type* DX assay broadly. I use it for approximately 90% of my patients with node-negative breast cancer. For node-positive disease, I use it often for patients with 1 to 3 positive lymph nodes. My preference would be to enroll these patients with node-positive disease in the SWOG-S1007 (RxPONDER) study, but I will occasionally order it even off study. I believe that the cancer biology rather than the nodal status is important. But I haven't made the jump to do it in patients with many positive lymph nodes because that's not currently accepted. However, I believe that's where we're heading.

**DR LOVE:** Would you talk about the Breast Cancer Index and how it can be used to predict risk of recurrence and the benefit of extended adjuvant therapy?

**DR O'REGAN:** The Breast Cancer Index is a combination of the endocrine response biomarker H/I (HoxB13/IL17BR) and the 5-gene molecular grade index. This is the one molecular assay that has been shown to be able to predict which patients with ER-positive, node-negative breast cancer will benefit from extended adjuvant endocrine treatment. The caveat is that it was based on the MA.17 trial in which patients received tamoxifen and were transitioned to letrozole (Sgroi 2013a).

The Breast Cancer Index was also able to predict the risk of recurrence up to 10 years. Up front, like the Recurrence Score, patients can be classified into 3 risk groups — low, intermediate and high. When determining recurrence risk at 5 to 10 years, 2 groups of patients can be identified: the low-risk group is one and the intermediate- and high-risk groups come together. Patients in the intermediate- and high-risk group are more likely to experience a recurrence in years 5 to 10 versus the low-risk group (Sgroi 2013b).

I usually use the Breast Cancer Index to explain to patients why it's important to stay on endocrine therapy rather than to tell them they don't need more endocrine therapy because I'm a little cautious about that.

**DR LOVE:** Would you discuss the study you presented at ASCO 2015 evaluating the Breast Cancer Index in patients with ER-positive, HER2-positive breast cancer for risk of late recurrence and benefit of extended endocrine therapy?

**DR O'REGAN:** Before this study, I had always believed that patients with ER-positive, HER2-positive breast cancer who made it to 5 years were unlikely to experience recurrence. This study showed that compared to patients with HER2-negative breast cancer, those with HER2-positive disease had a higher risk of recurrence during years 5 to 10. Also, more patients with HER2-positive tumors benefited from extended endocrine therapy than those in the HER2-negative group (O'Regan 2015; [4.1]).

I hadn't considered using the Breast Cancer Index for patients with ER-positive, HER2-positive breast cancer before this study, but these results indicate that it may

**4.1**

**Evaluation of the Breast Cancer Index (BCI) to Assess Risk of Late Recurrence and Potential Extended Endocrine Therapy (EET) Benefit for Patients with ER-Positive, HER2-Positive Breast Cancer**

| BCI risk classification | HER2-positive cohort (n = 140) | HER2-negative cohort (n = 1,042) |
|---|---|---|
| **BCI prognostic** | **Risk of late recurrence** | |
| Low | 13% | 54% |
| High | 87% | 46% |
| **BCI predictive** | **Likelihood of benefit from EET** | |
| Low | 32% | 62% |
| High | 68% | 38% |

**Conclusions:**

- BCI classified a higher proportion of HER2-positive/HR-positive tumors as being associated with high risk for late recurrence and a high likelihood of benefitting from EET compared to those that are HER2-negative/HR-positive. However, a subset of HER2-positive tumors are classified as low risk for late recurrence by BCI.
- A significant proportion of the HER2-positive cohort was predicted to benefit from EET.

O'Regan R et al. *Proc ASCO* 2015;**Abstract 595**.

be helpful in determining which of these patients should continue endocrine therapy beyond 5 years.

## Tracks 6-7

**DR LOVE:** The CDK4/6 inhibitor palbociclib recently received accelerated approval for use as first-line therapy in combination with letrozole for postmenopausal women with ER-positive, HER2-negative mBC. Would you discuss your clinical experience with this agent?

**DR O'REGAN:** A side effect of concern with palbociclib is neutropenia (Turner 2015). Serious infections can occur. If we administer it in the first-line setting, patients must come in for blood counts by day 15. It's now also recommended that blood counts be checked on day 21 of the first cycles so that the dose can be adjusted if necessary.

A certain subset of patients probably do not need palbociclib in the first-line setting and would fare well with endocrine therapy. We need to define who those patients are because we are changing the whole game plan for them now.

**DR LOVE:** In what situations would you use palbociclib for a postmenopausal woman who experiences relapse while receiving an adjuvant AI?

**DR O'REGAN:** The disease-free interval would be the important determining factor. If a patient experienced relapse within 1 or 2 years, I would consider palbociclib. For a late recurrence, I might consider endocrine therapy alone, particularly for an older patient, although we have not observed any indication that older patients experience more toxicity. So for patients with de novo metastatic disease or patients who have a long disease-free interval, I would consider holding palbociclib until later.

**DR LOVE:** Beyond the first-line setting, how do you incorporate palbociclib versus everolimus in your practice?

**DR O'REGAN:** I would tend to use palbociclib before everolimus because the efficacy data support palbociclib. That agent has shown positive results in the first-line setting, and we do not have the data with everolimus. However, for a patient who experiences relapse after having received a nonsteroidal AI in the adjuvant setting, either of them could be administered. Palbociclib is not approved outside the first-line setting, so that would be another consideration, although I haven't had a problem obtaining approval since the ASCO meeting. ■

## SELECT PUBLICATIONS


Finn RS et al. **The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study.** *Lancet Oncol* 2015;16(1):25-35.

O'Regan R et al. **Evaluation of the Breast Cancer Index in patients with HER2+/HR+ breast cancer for risk of late recurrence and potential extended endocrine benefit.** *Proc ASCO* 2015;**Abstract 595**.

Sgroi D et al. **Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker.** *J Natl Cancer Inst* 2013a;105(14):1036-42.

Sgroi D et al. **Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population.** *Lancet Oncol* 2013b;14(11):1067.

Turner NC et al. **Palbociclib in hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2015;373(3):209-19.

**QUESTIONS (PLEASE CIRCLE ANSWER):**

1. **In the PALOMA-3 trial evaluating the addition of palbociclib to fulvestrant for patients with ER-positive, HER2-negative advanced breast cancer, the most common Grade 3 or 4 adverse event reported was _____.**
   a. Neutropenia
   b. Thrombocytopenia
   c. Fatigue

2. **Which of the following CDK4/6 inhibitors has demonstrated a significant response rate as a single agent in ER-positive mBC?**
   a. Abemaciclib
   b. Palbociclib
   c. Ribociclib

3. **Mucositis and fatigue are adverse events commonly associated with the administration of _____.**
   a. Eribulin
   b. Everolimus
   c. Both a and b
   d. Neither a nor b

4. **The Phase II ADAPT trial evaluating neoadjuvant T-DM1 for 12 weeks with or without endocrine therapy in ER-positive, HER2-positive early breast cancer demonstrated _____.**
   a. A pCR rate of more than 40% in patients who received T-DM1
   b. Adding endocrine therapy to T-DM1 increases the rate of pCR in pre- and postmenopausal patients
   c. Both a and b

5. **The Phase III MARIANNE study of T-DM1 with or without pertuzumab versus trastuzumab with a taxane as first-line therapy for HER2-positive mBC demonstrated a significant improvement in PFS with T-DM1.**
   a. True
   b. False

6. **The ongoing Phase II KEYNOTE-086 trial is examining pembrolizumab monotherapy in the treatment of _____ mTNBC.**
   a. PD-L1-positive
   b. PD-L1-negative
   c. Both a and b

7. **Which of the following statements is true about the results of the Phase II MDV3100-11 trial of enzalutamide for patients with advanced AR-positive TNBC?**
   a. AR positivity was determined using the "PREDICT AR" gene expression assay
   b. Enzalutamide had clinical activity in patients with AR-positive TNBC
   c. Safety data were consistent with the known profile of enzalutamide
   d. All of the above

8. **In the Phase II single-arm study of eribulin in combination with trastuzumab as first-line therapy for patients with locally recurrent or metastatic HER2-positive breast cancer, treatment resulted in _____.**
   a. An objective response rate of approximately 70%
   b. Peripheral neuropathy (all grades) in about 70% of patients
   c. Both a and b
   d. Neither a nor b

9. **The CDK4/6 inhibitor palbociclib recently received accelerated approval for use in combination with letrozole as treatment for postmenopausal women with ER-positive, HER2-negative mBC in the _____ setting.**
   a. First-line
   b. Second-line
   c. Late-line

10. **A recent study by O'Regan and colleagues evaluating the Breast Cancer Index in patients with tumors that were ER-positive and HER2-positive demonstrated that individuals with these tumors had _____ versus those who had HER2-negative disease.**
    a. A higher incidence of late risk of recurrence
    b. A higher likelihood of benefitting from extended endocrine therapy
    c. Both a and b
    d. Neither a nor b

## EDUCATIONAL ASSESSMENT AND CREDIT FORM

### *Breast Cancer Update* — Issue 2, 2015

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

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

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

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

| | BEFORE | AFTER |
|---|---|---|
| ADAPT: Results of a Phase II trial of neoadjuvant T-DM1 with or without endocrine therapy in ER-positive, HER2-positive early breast cancer | 4 3 2 1 | 4 3 2 1 |
| Use of the Breast Cancer Index assay to predict the risk of recurrence and benefit of extended endocrine therapy | 4 3 2 1 | 4 3 2 1 |
| Recent data with novel agents under investigation (eg, checkpoint inhibitors, AR antagonists) for TNBC | 4 3 2 1 | 4 3 2 1 |
| Response of patients with HER2-positive IBC to HER2-targeted therapies | 4 3 2 1 | 4 3 2 1 |
| Activity and tolerability of CDK4/6 inhibitors for ER-positive mBC | 4 3 2 1 | 4 3 2 1 |
| Efficacy and safety of eribulin in combination with trastuzumab as first-line therapy for locally recurrent or metastatic, HER2-positive breast cancer | 4 3 2 1 | 4 3 2 1 |

**Practice Setting:**

☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice
☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

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

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

☐ Yes ☐ No If no, please explain:.....

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

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

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

.....

.....

.....

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

☐ Yes ☐ No
If no, please explain:.....

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

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

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

- Develop an evidence-based algorithm for the treatment of hormone-sensitive advanced BC, including the use of endocrine, chemotherapeutic and biologic agents. .....4 3 2 1 N/M N/A
- Implement a long-term clinical plan for the management of metastatic HER2-positive BC, incorporating existing, recently approved and investigational targeted treatments. .....4 3 2 1 N/M N/A
- Evaluate available and emerging data guiding the use of genomic assays to optimize decision-making regarding adjuvant chemotherapy and extended endocrine therapy. .....4 3 2 1 N/M N/A
- Appraise novel treatment strategies under investigation in advanced BC (eg, anti-PD-1/PD-L1 antibodies, androgen receptor inhibitors). .....4 3 2 1 N/M N/A
- Apply the results of current clinical data to the management of triple-negative BC. .....4 3 2 1 N/M N/A
- Develop a plan of care for patients with advanced inflammatory BC, incorporating existing and novel treatment approaches. .....4 3 2 1 N/M N/A

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

.....

.....

**Would you recommend this activity to a colleague?**

☐ Yes ☐ No

If no, please explain: .....

**Additional comments about this activity:**

.....

.....

.....

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

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

| Faculty | Knowledge of subject matter | Effectiveness as an educator |
|---|---|---|
| Beth Overmoyer, MD | 4 3 2 1 | 4 3 2 1 |
| Sandra M Swain, MD | 4 3 2 1 | 4 3 2 1 |
| Joyce O'Shaughnessy, MD | 4 3 2 1 | 4 3 2 1 |
| Ruth M O'Regan, MD | 4 3 2 1 | 4 3 2 1 |
| **Editor** | **Knowledge of subject matter** | **Effectiveness as an educator** |
| Neil Love, MD | 4 3 2 1 | 4 3 2 1 |

**Please recommend additional faculty for future activities:**

.....

**Other comments about the faculty and editor for this activity:**

.....

.....

.....

## REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

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# Breast Cancer® UPDATE

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Release date: January 2016
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