BCU | 2014 VOL 13 | ISSUE 2

Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Ann H Partridge, MD, MPH
Clifford Hudis, MD
John Crown, BCh, BAO, BSc, MD, MBA
Claudine Isaacs, MD

EDITOR

Neil Love, MD

CONTENTS

2 Audio CDs
Monograph

CME Certified

Subscribe to Podcasts or download MP3s of this program at ResearchToPractice.com/BCU214

Follow us at Facebook.com/ResearchToPractice Follow us on Twitter @DrNeilLove

Breast Cancer Update

A Continuing Medical Education Audio Series

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.
- Recall the recent FDA approval of neoadjuvant pertuzumab, and consider this therapeutic approach when evaluating appropriate patients with HER2-positive early breast cancer.
- Formulate individualized approaches to first- and later-line therapy for patients with HER2-negative metastatic breast cancer.
- Develop an evidence-based algorithm for the initial and long-term treatment of localized hormone receptor-positive pre- and postmenopausal breast cancer.
- Recognize the evolving application of biomarkers and multigene assays in breast cancer management, and effectively use these tools to refine or individualize treatment plans for patients.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should review the CME information, listen to the CDs, review the monograph, complete the Post-test with a score of 70% or better and fill out the Educational Assessment and Credit Form located in the back of this monograph or on our website at **ResearchToPractice.com/BCU214/CME**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/BCU214** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated within the text of the monograph in **blue, bold text**.

This activity is supported by educational grants from Eisai Inc, Genentech BioOncology, Genomic Health Inc and Novartis Pharmaceuticals Corporation.

Release date: October 2014; Expiration date: October 2015

TABLE OF CONTENTS

FACULTY INTERVIEWS

3 **Ann H Partridge, MD, MPH**
Director, Adult Survivorship Program
Founder and Director, Program for Young Women with Breast Cancer
Dana-Farber Cancer Institute
Associate Professor of Medicine, Harvard Medical School
Boston, Massachusetts

7 **Clifford Hudis, MD**
Chief, Breast Medicine Service
Solid Tumor Division
Department of Medicine
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

11 **John Crown, BCh, BAO, BSc, MD, MBA**
Consultant Medical Oncologist
St Vincent's University Hospital
Dublin, Ireland

15 **Claudine Isaacs, MD**
Professor of Medicine and Oncology
Co-Director, Breast Cancer Program
Lombardi Comprehensive Cancer Center
Georgetown University
Washington, DC

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

EDITOR

Neil Love, MD
Research To Practice
Miami, Florida

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — **Drs Partridge** and **Hudis** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Crown** — Speakers Bureau: Merck, Novartis Pharmaceuticals Corporation; Other Remunerated Activities: Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Novartis Pharmaceuticals Corporation, Pfizer Inc. **Dr Isaacs** — Consulting Agreement: Novartis Pharmaceuticals Corporation; Contracted Research: Novartis Pharmaceuticals Corporation, Pfizer Inc; Speakers Bureau: Celgene Corporation, Genentech BioOncology.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals Inc, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc, Teva Oncology and VisionGate Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

Have Questions or Cases You Would Like Us to Pose to the Faculty?

Submit them to us via Facebook or Twitter
and we will do our best to get them answered for you

Facebook.com/ResearchToPractice or Twitter @DrNeilLove

INTERVIEW

Ann H Partridge, MD, MPH

Dr Partridge is Director of the Adult Survivorship Program and Founder and Director of the Program for Young Women with Breast Cancer at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-14

Track 1 Results of the Phase II APT study of adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer (BC)

Track 2 Comparative toxicity profiles of paclitaxel/trastuzumab, TCH and anthracycline-containing regimens as adjuvant therapy for HER2-positive BC

Track 3 ATEMPT: A Phase II trial of T-DM1 versus paclitaxel and trastuzumab for Stage I HER2-positive BC

Track 4 Clinical trials incorporating T-DM1 into the adjuvant setting

Track 5 **Case discussion:** A 36-year-old pregnant woman with a 3-cm, high-grade, triple-negative invasive ductal carcinoma (IDC)

Track 6 Pregnancy and anti-HER2 directed therapies

Track 7 Results of CALGB-40603: Addition of carboplatin alone or in combination with bevacizumab to neoadjuvant weekly paclitaxel → dose-dense AC for triple-negative BC (TNBC)

Track 8 INFORM: A Phase II trial of neoadjuvant cisplatin versus AC for patients with newly diagnosed BC and germline BRCA mutations

Track 9 **Case discussion:** A 38-year-old woman with a history of Hodgkin lymphoma and tonsillar cancer presents with low-grade, ER/PR-positive, HER2-negative IDC with 1 of 5 positive sentinel nodes and a 21-gene Recurrence Score® of 10

Track 10 Perspective on the use of the 21-gene Recurrence Score assay for ER-positive, HER2-negative BC

Track 11 Continuing adjuvant tamoxifen to 10 years versus stopping at 5 years

Track 12 Viewpoint on the meta-analysis evaluating the effects of bisphosphonates on recurrence and cause-specific mortality in patients with early BC

Track 13 **Case discussion:** A 42-year-old woman with Stage III, high-grade, ER/PR-positive, HER2-negative IDC with diffuse bony metastases

Track 14 ASCO Clinical Practice Guidelines for patients with HER2-negative metastatic BC (mBC)

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you discuss the Phase II APT trial that your group presented at the 2013 San Antonio Breast Cancer Symposium evaluating adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer (Tolaney 2013)?

DR PARTRIDGE: The APT trial was designed to ascertain the potential value of trastuzumab for women with lower-risk HER2-positive breast cancer. Much thought went into the design of this trial. We never would have been able to perform a prospective randomized trial of trastuzumab-based therapy in this setting because it would take 20 years to obtain all the data. So the main considerations were to design a study that

would be able to accrue patients while providing some information to inform care. In the end this study accrued more than 400 patients, and the results turned out to be a boon for the whole cancer community. The rate of recurrence overall was extremely small. A total of 10 recurrence events occurred, and only 2 distant recurrence events were reported at a median follow-up of approximately 3 years. Most of the events were contralateral or a recurrence in the ipsilateral breast. We need to continue to observe these patients over time.

DR LOVE: How does the tolerability of this regimen compare to other regimens that are typically used in this setting?

DR PARTRIDGE: I've administered all of the various anti-HER2 regimens to numerous patients, and the toxicities are like night and day. We're all familiar with the low but serious risk of cardiotoxicity and the secondary leukemia risk associated with anthracyclines and the AC regimen. Docetaxel/carboplatin and trastuzumab (TCH) is a good alternative but is extraordinarily toxic in terms of quality of life because of the neutropenia, fatigue, nausea and neuropathy that many women experience.

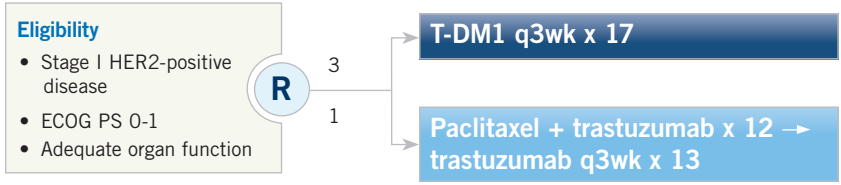
We did not observe the same levels of risk in terms of long-term, late side effects with paclitaxel/trastuzumab. Some neuropathy was observed, in addition to other quality-of-life side effects such as fatigue, but in my clinical experience the incidence was not remotely as high as one would anticipate with one of the more standard, "kitchen-sink regimens" as I like to call them.

A follow-up study to the APT trial called ATEMPT is evaluating T-DM1 versus paclitaxel/trastuzumab for patients with Stage I HER2-positive breast cancer (1.1). This exciting trial was designed to further reduce toxicity and potentially improve efficacy for patients with low-risk HER2-positive disease. I believe T-DM1 is the beginning of what I hope to be an explosion of therapies that will allow us to have excellent disease control in the adjuvant setting while not wreaking havoc on the rest of the body.

1.1

ATEMPT: A Phase II Trial of T-DM1 versus Paclitaxel and Trastuzumab for Stage I HER2-Positive Breast Cancer

Protocol ID: NCT01853748 **Target Accrual:** 500



Adjuvant endocrine therapy (if applicable) may be initiated after completion of 12 weeks of therapy. Adjuvant radiation therapy may be administered concurrently with study treatment.

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

Track 6

DR LOVE: You are very involved in programs targeting young women with breast cancer. What is known about the safety of anti-HER2 directed therapies during pregnancy?

DR PARTRIDGE: A registry called MotHER is currently tracking all in-utero exposures to trastuzumab and pertuzumab, and a poster on this program was presented at ASCO 2013 (Brown 2013).

Currently trastuzumab includes a black box warning, as does pertuzumab, which contraindicates use during pregnancy because of reports of oligohydramnios, which is less fluid than you'd like in the amniotic sac. This phenomenon can lead to poor fetal outcomes, including fetal demise, so avoidance of those antibody therapies is prudent at this time (Sarno 2013; [1.2]).

Does that mean that exposure to trastuzumab in utero is a guaranteed cause of oligohydramnios? No, and some reports demonstrate that babies are being delivered safely after exposure to trastuzumab. However, in general we would not want to expose a fetus to it at this point. I am not aware of any reports of T-DM1 exposure in utero, but it sounds like a bad idea and not one I'd want to test.

1.2

Use of Trastuzumab as Breast Cancer Therapy During Pregnancy

"Monoclonal antibodies are the cornerstone of the treatment of several types of tumors, but their use in pregnant women is not clearly defined … Trastuzumab administration has been associated with an elevated incidence of oligohydramnios and poor neonatal outcomes, particularly when prescribed after the first trimester for repeated infusions, and therefore it is not recommended … Few data are available about other [monoclonal antibodies], and hence their use during pregnancy remains discouraged."

Sarno MA et al. *Immunotherapy* 2013;5(7):733–41.

Track 10

DR LOVE: The 21-gene Recurrence Score is now widely used for patients with ER-positive, HER2-negative, node-negative tumors. In what situations, if any, do you employ this assay in patients with positive nodes?

DR PARTRIDGE: I consider ordering the assay for an older patient with a few positive nodes — à la the SWOG trial reported by Dr Kathy Albain, which analyzed the use of the 21-gene Recurrence Score assay for patients with 1 to 3 positive nodes (Albain 2010). Above that level of nodal involvement the risks are higher and it's much harder to justify not administering chemotherapy. However, some uncertainty persists. We await the ultimate RxPONDER trial results (NCT01272037).

My threshold for administering chemotherapy is probably a little lower for younger patients, although I try not to base treatments on age. Such patients will have ovarian function for a long time, so I consider that. But more important is how chemotherapy averse the person is and how much benefit I believe it will add. I order a 21-gene Recurrence Score only when I'm ambivalent about the decision.

In terms of patients with negative nodes, if a patient presents with a T1a tumor, I do not administer chemotherapy as a rule, with rare exceptions, no matter how big the tumor is, so I don't order a 21-gene Recurrence Score. If a person comes in with an 8-cm tumor, unless the patient is older or it's a low-grade tumor and there is some reason not to administer chemotherapy, or multiple positive lymph nodes are detected, I don't order a Recurrence Score assay because I will be administering chemotherapy in that setting.

The assay comes into play in the in-between situations, and what I tell patients is, I'm ordering this assay because I believe you have a "sheep" and I'm trying to see if it's a "wolf in sheep's clothing." So I don't order a Recurrence Score if I believe you have a "wolf" and I don't order it if I know you have a "sheep." I order it only when I believe you have a "sheep" and I want to make sure it's not a "wolf."

Track 11

DR LOVE: How do you approach the issue today in your practice of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years for patients with ER-positive early breast cancer?

DR PARTRIDGE: I believe it's not quite the knee-jerk, "no-brainer" that many interpreted from the data (Davies 2013; Gray 2013). The problem of whether to extend endocrine therapy beyond 5 years is driven by the original risk of the disease, so anybody who was at higher risk of recurrence in the first 5 years is generally at higher risk of recurrence in the second 5 years and beyond. Then it's driven by how well they tolerate the therapy, what stage of life they they are at and how much additional risk reduction they want compared to tolerating the side effects, if any.

It's a highly individual decision based on all of those factors. It is also dependent on age because as women age their risk of serious adverse events from tamoxifen, such as blood clots and cancer of the uterus, increases. When I consult with younger patients, I say, "We'll talk about it. Right now the standard is 5, but we could consider 10." Notice my semantics. I say the standard is 5 years. Can the standard be 10 years right now? Sure. We have 2 randomized trials that say 10 is better, but I find clinically that when I tell patients they are to receive 10 years of hormonal therapy, some feel as though I've sentenced them to a 10-year jail sentence. I don't find that this works emotionally.

So I say, "We're going to treat for 5 years at a minimum and then let's talk about whether or not it makes sense for you to do more." I find that much easier to swallow for those patients, and it's the reality because some of these patients will stop therapy earlier because of intolerance, and some may change their mind over time about how they feel about tamoxifen. I believe some women view tamoxifen as their power pill and some women view it as a jail sentence, and that can have huge implications for whether they even take it and how well they tolerate it. ■

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.

Brown V et al. **MotHER: A registry for women with breast cancer who received trastuzumab (T) with or without pertuzumab (P) during pregnancy or within 6 months prior to conception.** *Proc ASCO* 2013;**Abstract TPS658**.

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

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

Sarno MA et al. **Are monoclonal antibodies a safe treatment for cancer during pregnancy?** *Immunotherapy* 2013;5(7):733-41.

Zagouri F et al. **Trastuzumab administration during pregnancy: A systematic review and meta-analysis.** *Breast Cancer Res Treat* 2013;137(2):349-57.

INTERVIEW

Clifford Hudis, MD

Dr Hudis is Chief of the Breast Medicine Service in the Solid Tumor Division of the Department of Medicine at Memorial Sloan Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-10

Track 1 Utility of the 21-gene Recurrence Score versus other genomic assays for ER-positive, HER2-negative BC

Track 2 Ongoing Phase II feasibility study of dose-dense AC followed by eribulin with or without prophylactic growth factors as adjuvant therapy for early-stage, HER2-negative BC

Track 3 Results of an FDA-led meta-analysis evaluating trials of neoadjuvant systemic therapy for BC

Track 4 Perspective on the recent FDA approval of neoadjuvant pertuzumab

Track 5 FDA label indication and the NCCN guidelines on the use of (neo)adjuvant pertuzumab

Track 6 Results of a joint analysis of the IBCSG TEXT and SOFT trials: Adjuvant exemestane with ovarian function suppression (OFS) versus tamoxifen with OFS for premenopausal women with ER-positive early BC

Track 7 Duration of adjuvant endocrine therapy in ER-positive BC

Track 8 Results of Intergroup SWOG-S0230/ POEMS (Prevention Of Early Menopause Study) of an LHRH analog during chemotherapy to reduce ovarian failure in early-stage, ER/PR-negative BC

Track 9 CALGB-40101: Results of a Phase III trial comparing AC to single-agent paclitaxel as adjuvant therapy for patients with BC and 0 to 3 positive axillary nodes

Track 10 Dose-dense versus nondose-dense chemotherapy in BC

Select Excerpts from the Interview

Tracks 3-5

DR LOVE: The FDA recently granted accelerated approval to pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early-stage breast cancer. What is your perspective on this approval?

DR HUDIS: Pertuzumab is an exciting new drug that demonstrated a dramatic improvement in progression-free and overall survival in CLEOPATRA, the first randomized trial of this agent in the metastatic setting. With the paucity of drugs that have been shown to improve survival in metastatic disease, optimism was high.

The adjuvant Phase III APHINITY trial evaluating the addition of pertuzumab to chemotherapy and trastuzumab for patients with HER2-positive primary breast cancer is now ongoing. The target accrual is approximately 5,000 patients, and the trial is powered to determine whether pertuzumab is beneficial in the adjuvant setting

(NCT01358877). I predict the results will be positive because the CLEOPATRA trial demonstrated such a significant benefit with pertuzumab.

Studies in the neoadjuvant setting, like the NEOSPHERE trial, reported a dramatic improvement in pathologic complete response (pCR) with the addition of pertuzumab (Gianni 2012). The question that arose was, does this improvement in pCR accurately predict long-term benefit? If it does, we will have a tremendous motivation to conduct a larger proportion of drug development studies in the neoadjuvant setting. The FDA weighed in on this, and a meta-analysis of clinical trials on neoadjuvant treatment for breast cancer was published. This study reported that an improvement in pCR does not correlate with an improvement in event-free and overall survival (Cortazar 2014).

The FDA has approved pertuzumab in the neoadjuvant setting for 3 to 6 cycles for patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer who have tumors larger than 2 centimeters or positive nodes. The problem is that by labeling the drug for the neoadjuvant setting and administering it for 3 to 6 cycles, we may only increase the pCR rate.

Shrinkage of the tumor to diminish the extent of surgery would be a benefit, but that would account for less than 10% of the cases. My passionate point of view is that if you're going to take a public health gamble with all the expense that's involved, you may as well gamble with what the APHINITY trial is testing in the adjuvant setting and administer the pertuzumab for a year.

DR LOVE: The NCCN considers it reasonable to incorporate pertuzumab as part of an adjuvant regimen even though we do not have any data to support that practice and pertuzumab has not been approved by the FDA in that setting. Would you comment on this?

DR HUDIS: I'm espousing the point of view of the NCCN, which is that if you were eligible to receive neoadjuvant pertuzumab, why should you be denied the agent simply because you saw a surgeon first? The vagaries of the referral pattern bother me. Only certain patients would receive neoadjuvant pertuzumab, depending on which specialist saw them first. They could not be offered the drug in the adjuvant setting off label. I would consider pertuzumab in the adjuvant setting for a year for patients who would be eligible for the drug preoperatively.

If the FDA wanted to grant pertuzumab accelerated approval, this approval should have included its use in the adjuvant setting also. If the APHINITY trial is negative, the approval could be withdrawn — the accelerated approval of pertuzumab in the neoadjuvant setting is contingent on APHINITY being positive.

Track 6

DR LOVE: What are your thoughts on the joint analysis of the SOFT and TEXT trials comparing adjuvant exemestane with ovarian function suppression to tamoxifen with ovarian function suppression for premenopausal women with ER-positive early breast cancer?

DR HUDIS: The results of the SOFT and TEXT trials demonstrated statistically significant improvements in disease-free survival and the rate of freedom from breast cancer with exemestane and ovarian suppression compared to tamoxifen and ovarian suppression (Pagani 2014; [2.1]). This could motivate a change in practice, although the differ-

ence in overall survival between the 2 arms was not statistically significant. The big question as to whether the addition of ovarian function suppression to hormone therapy is beneficial has still not been answered definitively with this analysis. The results from the control arm of tamoxifen alone were not included in this study.

2.1

Joint Analysis of the TEXT and SOFT Trials: Adjuvant Exemestane with Ovarian Function Suppression (OFS) versus Tamoxifen with OFS for Premenopausal Women with ER-Positive Early Breast Cancer (BC)

Efficacy*	Exemestane + OFS (n = 2,346)	Tamoxifen + OFS (n = 2,344)	Hazard ratio	*p*-value
Five-year disease-free survival	91.1%	87.3%	0.72	<0.001
Rate of freedom from BC at 5 years	92.8%	88.8%	0.66	<0.001
Overall survival	95.9%	96.9%	1.14	0.37

Adverse events

- Select adverse events of Grade 3 or 4 were reported for 30.6% of the patients in the exemestane + OFS group and 29.4% of those in the tamoxifen + OFS group, with profiles similar to those for postmenopausal women.
- Patients in the exemestane + OFS arm reported significantly more detrimental effects of bone or joint pain and vaginal dryness and a greater loss of sexual interest, whereas those in the tamoxifen + OFS group were significantly more affected by hot flashes and vaginal discharge.

* Median follow-up = 68 months

Pagani O et al. *N Engl J Med* 2014;371(2):107–18.

Track 8

DR LOVE: Would you discuss the Phase III POEMS/SWOG-S0230 study of goserelin and chemotherapy for early-stage, hormone receptor–negative breast cancer to reduce the risk of infertility from chemotherapy?

DR HUDIS: I believe that this study was, from a practical perspective, one of the most high-impact presentations at ASCO 2014. It asked an important lifestyle question: Do we have safe ways to preserve fertility for young patients whom we're trying to cure of breast cancer? Patients with hormone receptor–negative breast cancer were randomly assigned to receive standard chemotherapy with or without goserelin. The ovarian failure rate at 2 years and pregnancy outcomes for women in the 2 groups were compared.

The results clearly indicated that goserelin preserved ovarian function. The group that received goserelin had approximately twice as many pregnancies. Because the study size was small, one can't be sure that this result was related to the drug. Interestingly, a trend toward better clinical outcomes was also evident among the patients who were randomly assigned to receive goserelin (Moore 2014).

This is the first time that this approach has demonstrated consistent beneficial effects across multiple endpoints. We can now offer patients ovarian rest to maintain the premenopausal state. These results are practice changing for me. I believe that this study has implications well beyond breast cancer. It will provoke young people receiving chemotherapy to consider these agents.

Track 2

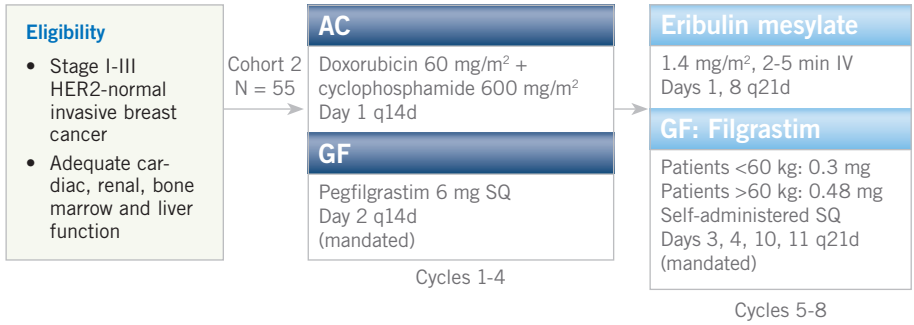
DR LOVE: Would you discuss the rationale for the ongoing Phase II study you're involved with evaluating dose-dense AC followed by eribulin as adjuvant therapy for early-stage HER2-negative breast cancer?

DR HUDIS: Eribulin was approved for previously treated metastatic breast cancer on the basis of its superiority to treatment of physician's choice. Although the difference in survival was modest, it was important because the primary endpoint was overall survival (Cortes 2011). Because eribulin improved survival in the metastatic setting, the hope was that it would be beneficial in the adjuvant setting. It is one of the few agents to have improved survival in metastatic disease, so it is worth investigating in the curative setting. The Phase II trial of AC followed by eribulin as adjuvant therapy for early breast cancer is a pilot study to move eribulin in that direction (Traina 2014; [2.2]). ■

2.2

Ongoing Phase II Study of Dose-Dense Doxorubicin and Cyclophosphamide (AC) Followed by Eribulin with or without Prophylactic Growth Factor (GF) as Adjuvant Treatment for Early-Stage Breast Cancer

Protocol ID: NCT01328249



SQ = subcutaneous

Primary objective: Determine feasibility of adjuvant AC for 4 cycles followed by eribulin for 4 cycles

- Cohort 1 with 55 enrolled patients who received treatment was closed. Without a prophylactic GF, the regimen was approaching nonfeasibility due to neutropenic events.
- Study was amended (cohort 2), and a prophylactic GF was required with eribulin.

Traina TA et al. *Proc ASCO* 2014;**Abstract TPS670**; **www.clinicaltrials.gov**. Accessed September 2014.

SELECT PUBLICATIONS

Cortazar P et al. **Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis.** *Lancet* 2014;384(9938):164-72.

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

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.

Moore HCF et al. **Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance).** *Proc ASCO* 2014;**Abstract LBA505**.

INTERVIEW

John Crown, BCh, BAO, BSc, MD, MBA

Dr Crown is Consultant Medical Oncologist at St Vincent's University Hospital in Dublin, Ireland.

Tracks 1-13

Track 1 CLEOPATRA trial: Improved survival with the addition of pertuzumab to trastuzumab/docetaxel as first-line therapy for HER2-positive mBC

Track 2 Overview of tolerability and efficacy of T-DM1 in mBC

Track 3 Rationale for the ongoing NSABP-B-50-I (KATHERINE) study: A Phase III trial of T-DM1 versus trastuzumab as adjuvant therapy for patients with HER2-positive BC who have residual tumor in the breast or axillary nodes after neoadjuvant treatment

Track 4 Sequencing of HER2-directed therapies in HER2-positive mBC

Track 5 Treatment for patients with HER2-positive BC and brain metastases

Track 6 Therapeutic options for patients who experience disease progression during adjuvant endocrine therapy

Track 7 Clinical experience with everolimus in mBC

Track 8 PALOMA-1: Results of a Phase II study of letrozole with or without the CDK4/6 inhibitor palbociclib as first-line therapy for ER-positive, HER2-negative mBC

Track 9 Prevention and management of everolimus-associated toxicities

Track 10 Efficacy and tolerability of eribulin in HER2-negative mBC

Track 11 Predictive value of the 21-gene Recurrence Score

Track 12 Use of the 21-gene Recurrence Score in the United States versus European countries

Track 13 Changes in physicians' treatment recommendations based on the 21-gene Recurrence Score

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: What are your thoughts about the new ASCO guidelines that recommend first-line therapy with the CLEOPATRA regimen of chemotherapy/trastuzumab/pertuzumab followed by second-line T-DM1 for patients with advanced HER2-positive breast cancer?

DR CROWN: First-line therapy with chemotherapy/trastuzumab/pertuzumab followed by second-line T-DM1 makes great sense. The guideline supports the available data. The more generic story that needs to be told is that the circumstantial evidence and, indeed, the trial-based evidence for continuing anti-HER2 therapy beyond first- and second-line treatment is getting stronger. However, in some parts of the world only 1 line of anti-HER2 therapy is approved.

Clearly the current and cleanest data for first-line therapy suggest that for patients for whom the chemotherapy backbone is appropriate, the right anti-HER2 therapy is

the combination of trastuzumab with pertuzumab. As second-line therapy, T-DM1 has been compared to capecitabine/lapatinib and found to be better and safer (Verma 2012).

DR LOVE: Where does lapatinib, particularly in combination with trastuzumab, a nonchemotherapy-based regimen, fit into the treatment sequence, especially for patients who would like to have a chemotherapy break or those who are ineligible for chemotherapy?

DR CROWN: It's a shame that a good, clean first-line study of chemotherapy/trastuzumab with or without lapatinib was not conducted early on, because the body of circumstantial evidence would suggest synergy between the 2 agents, which is clinically relevant. A study of lapatinib with or without trastuzumab for patients with trastuzumab-refractory HER2-positive disease indicated that trastuzumab continuation in combination with lapatinib was beneficial (Blackwell 2010).

This means that in addition to the individual benefit of each drug, synergy occurs when they are used together. For this reason, an ongoing European trial is evaluating chemotherapy and trastuzumab with or without lapatinib (NCT01526369). Even though the increasing availability of pertuzumab will complicate the completion of that trial, pertuzumab is still not available in many jurisdictions.

In most countries, the regulatory approval for lapatinib resides on its use with capecitabine. Some patients who may have received prior capecitabine may be ineligible for lapatinib/capecitabine. However, I have administered the combination of the 2 anti-HER2 therapies without chemotherapy and have seen patients experience a more prolonged degree of disease control.

DR LOVE: ASCO clinical practice guidelines also state that patients with advanced HER2-positive breast cancer and brain metastases should receive appropriate local and systemic therapy. For those receiving anti-HER2 therapy whose systemic disease is not progressing at the time of diagnosis of brain metastases, ASCO recommends that the systemic therapy should not be switched (Ramakrishna 2014). What would be your treatment approach for a patient who achieves a complete response after receiving the CLEOPATRA regimen in the first-line setting but develops brain metastases?

DR CROWN: I would treat the brain metastasis locally on its own merits, either with stereotactic radiosurgery or whole brain radiation therapy, depending on the anatomy of the disease. In general I tend to continue the trastuzumab and, if further problems arise, I add lapatinib.

Tracks 7, 9

DR LOVE: How do you typically use everolimus, which was approved on the basis of the BOLERO-2 trial that evaluated everolimus in combination with exemestane for patients with metastatic breast cancer (3.1)? Do you typically combine it with exemestane only or with other hormonal therapies?

DR CROWN: At this point the available data support its use with an aromatase inhibitor. I'm not particularly concerned about which aromatase inhibitor is selected. I believe that will often be a function of what the patient has been exposed to in the adjuvant setting. Also, issues of habit can arise on the part of the treating oncologist.

3.1

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

Clinical outcome	Exemestane + everolimus (n = 485)	Exemestane + placebo (n = 239)	Hazard ratio	*p*-value
Median PFS (central assessment)	11.0 mo	4.1 mo	0.38	<0.0001
Median PFS (investigator assessment)	7.8 mo	3.2 mo	0.45	<0.0001
ORR (central assessment)	12.6%	2.1%	—	—
Median overall survival*	31.0 mo	26.6 mo	0.89	0.14
	Exemestane + everolimus (n = 482)		Exemestane + placebo (n = 238)	
Select adverse events	All	Grade 3 or 4	All	Grade 3 or 4
Stomatitis	56%	8%	11%	1%
Fatigue	37%	4%	27%	1%
Cough	22%	1%	11%	0%
Dyspnea	18%	4%	9%	<2%
Pneumonitis	12%	3%	0%	0%

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

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

DR LOVE: Would you discuss your clinical experience with everolimus?

DR CROWN: It's so nice to be able to tell patients that they don't need chemotherapy yet and that we can try something else first. Many of my patients have experienced excellent control with everolimus, some with 10 or more months of disease control, clear-cut shrinkage and improvement in quality of life for those with symptomatic pulmonary and other metastases. It can be a useful treatment. Patients tend to know they're receiving everolimus compared to an aromatase inhibitor only. Stomatitis and fatigue are common side effects.

Track 8

DR LOVE: What are your thoughts on the efficacy and safety of the investigational CDK4/6 inhibitor palbociclib as first-line therapy for patients with metastatic breast cancer?

DR CROWN: I've been involved with palbociclib in recent years. Data from the Phase II PALOMA-1 trial of letrozole with or without palbociclib for patients with hormone receptor-positive, HER2-negative metastatic breast cancer are highly provocative and staggering (Finn 2014; [3.2]).

The progression-free survival doubled and a higher response rate was observed with the addition of palbociclib. These results have led to a large-scale randomized Phase III trial (3.3). Palbociclib is not toxic. It's a mild agent, and it's unlikely that we'll have much difficulty with it. ■

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

	P + L	L alone	Hazard ratio	*p*-value
Median PFS	20.2 mo	10.2 mo	0.488	0.0004
Median OS	37.5 mo	33.3 mo	0.813	0.2105
Best ORR*	43%	33%	NR	NR

PFS = progression-free survival; OS = overall survival; ORR = overall response rate; NR = not reported

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

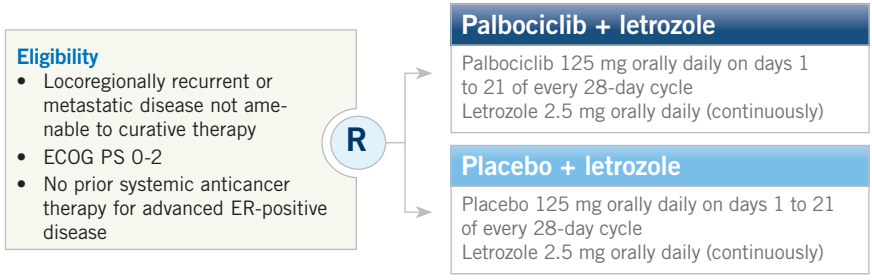
Conclusions: "P + L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P + L in this same mBC population is ongoing."

Finn RS et al. *Proc AACR* 2014;**Abstract CT101**; * Goodman A. *The ASCO Post* 2014;5(7).

3.3 PALOMA-2: A Phase III Trial Evaluating the Oral CDK4/6 Inhibitor Palbociclib with Letrozole versus Placebo with Letrozole as First-Line Therapy for Postmenopausal Patients with ER-Positive, HER2-Negative Advanced Breast Cancer

Protocol ID: NCT01740427

Target Accrual: 650



www.clinicaltrials.gov. Accessed October 2014.

SELECT PUBLICATIONS

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

Blackwell KL et al. **Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer.** *J Clin Oncol* 2010;28(7):1124-30.

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

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

Ramakrishna N et al. **Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline.** *J Clin Oncol* 2014;32(19):2100-8.

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

INTERVIEW

Claudine Isaacs, MD

Dr Isaacs is Professor of Medicine and Oncology and Co-Director of the Breast Cancer Program at Georgetown University's Lombardi Comprehensive Cancer Center in Washington, DC.

Tracks 1-12

Track 1 **Case discussion:** A 47-year-old woman with a 3.4-cm, poorly differentiated, triple-negative IDC

Track 2 Surgical clip placement for patients undergoing neoadjuvant chemotherapy for BC

Track 3 Adjuvant and neoadjuvant options for newly diagnosed TNBC

Track 4 NSABP-B-51: A Phase III trial evaluating radiation therapy in patients with positive axillary nodes prior to neoadjuvant chemotherapy that convert to pathologically negative axillary nodes after neoadjuvant chemotherapy

Track 5 Alliance A011202: An ongoing Phase III trial evaluating the role of axillary lymph node dissection for patients who have positive sentinel lymph node disease after neoadjuvant chemotherapy

Track 6 Approach to administering neoadjuvant therapy for patients with HER2-positive BC

Track 7 NSABP-B-50-I (KATHERINE): A Phase III trial of T-DM1 versus trastuzumab as adjuvant therapy for patients with HER2-positive BC who have residual tumor in the breast or axillary nodes after neoadjuvant treatment

Track 8 Viewpoint on the results of a joint analysis of the IBCSG TEXT and SOFT trials evaluating adjuvant exemestane with ovarian suppression in premenopausal BC

Track 9 **Case discussion:** A 40-year-old woman with a 2-cm, ER/PR-positive, HER2-negative, node-negative IDC and a 21-gene Recurrence Score of 12

Track 10 Use of the 21-gene Recurrence Score to guide adjuvant chemotherapy decision-making for patients with limited nodal involvement

Track 11 **Case discussion:** A 58-year-old woman with de novo metastatic ER/PR-positive, HER2-negative IDC

Track 12 Perspective on the results of 2 randomized Phase III trials evaluating primary tumor resection for patients with mBC

Select Excerpts from the Interview

Track 7

DR LOVE: Can you talk about the ongoing NSABP-B-50-I trial of T-DM1 versus trastuzumab for patients with residual disease at surgery after receiving preoperative systemic treatment (4.1)?

DR ISAACS: That is an interesting and important trial. I view residual disease after neoadjuvant chemotherapy differently in patients with hormone receptor-positive and hormone receptor-negative breast cancer. For patients with hormone receptor-positive disease, it is important to inform them that whether or not they achieve a pCR is not as clinically significant. The trial will determine whether T-DM1 is better than

trastuzumab and will be worthwhile for patients with HER2-positive disease with significant residual tumors.

4.1

NSABP-B-50-I (KATHERINE): Ongoing Phase III Trial Evaluating T-DM1 versus Trastuzumab as Adjuvant Therapy for Patients with HER2-Positive Primary Breast Cancer with Pathologic Residual Tumor in the Breast or Axillary Lymph Node After Preoperative Therapy

Protocol ID: NCT01772472

Target Accrual: 1,484

Eligibility

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

R

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

Trastuzumab (IV)
6 mg/kg every 3 weeks for 14 cycles

www.clinicaltrials.gov. Accessed September 2014.

Track 12

DR LOVE: Would you discuss the results of the 2 randomized Phase III trials presented at the 2013 San Antonio Breast Cancer Symposium evaluating the role of locoregional therapy for women presenting with de novo Stage IV disease?

DR ISAACS: One of the trials was conducted in India, and it evaluated women with complete or partial responses to first-line chemotherapy (Badwe 2013; [4.2]). These patients were randomly assigned to locoregional therapy or no locoregional therapy, and the trial produced no difference in overall survival. The issue with this study is that none of the women with HER2-positive disease received HER2-targeted therapy. We know what a profound effect that has on treatment outcome. Also, it was not a

4.2

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

Study design	Tata Memorial (India)[1] (n = 350)	MF 07-01 (Turkey)[2] (n = 293)
Initial systemic therapy before randomization	CEF with or without a taxane	None
Primary endpoint	Overall survival	Overall survival
Efficacy		
Overall survival	LRT vs no LRT HR 1.04, $p = 0.79$	Surgery vs systemic therapy HR 0.76, $p = 0.20$
Bone-only metastases	HR 1.43, p = NR	HR 0.60, $p = 0.15$
Solitary bone metastasis	NR	HR 0.23, $p = 0.02$

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

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

big trial, with only 350 enrolled patients. One of the questions regarding the trial is whether the approach applies to our current standard, especially for patients with HER2-positive disease.

The other Phase III trial was from Turkey (Soran 2013; [4.2]). It randomly assigned women who were diagnosed at presentation with metastatic disease to up-front systemic therapy with or without locoregional therapy. Thereafter, patients who received systemic therapy only were allowed to undergo locoregional therapy if the treating physician or healthcare team decided that it was needed for palliation. A 4-month improvement in overall survival was found for women who received up-front locoregional therapy, although the difference was not statistically significant.

The results suggested a benefit for those with a solitary bone metastasis. I believe that an issue with the Turkish trial is that not all the women from whom biopsies were obtained had bone metastases. Perhaps some had bone islands or benign masses.

It is clear from these 2 trials that we need to temper our enthusiasm for locoregional therapy. There is no question about that. In the United States I believe we had a tendency to favor surgery for these women before the results of the Indian and Turkish trials were presented.

Although the 2 trials produced negative results and did not definitely answer the question about the benefits of up-front locoregional therapy for Stage IV disease, the results should encourage us to enroll patients in the ongoing clinical trials that will more definitively answer the question. The ongoing ECOG-E2108 trial will address the question of whether early surgery is more effective than palliative therapy for patients with metastatic breast cancer (4.3). ■

4.3

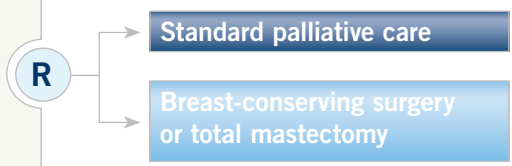
ECOG-E2108: Ongoing Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Protocol ID: NCT01242800

Target Accrual: 880

Eligibility

- Intact, invasive breast cancer (Stage IV disease)
- Involvement of at least 1 organ system with distant metastatic disease
- No recurrent disease
- No synchronous contralateral breast cancer



Khan SA. San Antonio Breast Cancer Symposium 2013. No abstract available; **www.clinicaltrials.gov**. Accessed September 2014.

SELECT PUBLICATIONS

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

Khan SA. **Does primary tumor resection improve survival for patients with Stage IV breast cancer?** San Antonio Breast Cancer Symposium 2013. No abstract available

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase II ATEMPT trial is evaluating _____ versus paclitaxel and trastuzumab for patients with Stage I HER2-positive breast cancer.**
   a. TCH
   b. T-DM1
   c. Palbociclib
   d. All of the above

2. **Results from the Phase III POEMS/SWOG-S0230 study of goserelin and chemotherapy for early-stage, hormone receptor-negative breast cancer indicated that goserelin use led to _____.**
   a. Better preservation of ovarian function
   b. Approximately twice as many pregnancies
   c. Both a and b
   d. Neither a nor b

3. **A joint analysis of the TEXT and SOFT trials evaluating adjuvant exemestane versus tamoxifen, each with ovarian function suppression, for premenopausal women with ER-positive early breast cancer demonstrated a significant benefit in _____ on the exemestane arm.**
   a. Disease-free survival at 5 years
   b. Rate of freedom from breast cancer at 5 years
   c. Overall survival
   d. Both a and b

4. **The FDA recently granted accelerated approval to pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early-stage breast cancer (tumor larger than 2 centimeters or node-positive).**
   a. True
   b. False

5. **The ongoing _____ trial is evaluating the addition of pertuzumab to chemotherapy/trastuzumab as adjuvant therapy for HER2-positive primary breast cancer.**
   a. APHINITY
   b. CLEOPATRA
   c. NEOSPHERE

6. **The results of the Phase III BOLERO-2 trial of exemestane with or without everolimus for patients with hormone receptor-positive metastatic breast cancer refractory to nonsteroidal aromatase inhibitors demonstrated a statistically significant improvement in _____ with everolimus.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b

7. **The final results of the randomized Phase II PALOMA-1 trial evaluating letrozole with or without palbociclib as first-line therapy for patients with ER-positive, HER2-negative metastatic breast cancer demonstrated a statistically significant improvement in _____ with palbociclib combined with letrozole.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above

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

9. **The ongoing ECOG-E2108 Phase III trial is comparing _____ to breast-conserving surgery or total mastectomy for intact primary tumors in patients with metastatic breast cancer without recurrent disease.**
   a. Standard palliative care
   b. Chemotherapy
   c. Surgery in combination with systemic therapy

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 2, 2014

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

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

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

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

	BEFORE	AFTER
ATEMPT: A Phase II trial of T-DM1 versus paclitaxel and trastuzumab for Stage I HER2-positive breast cancer	4 3 2 1	4 3 2 1
Differences between FDA label indication and the NCCN guidelines on the use of (neo)adjuvant pertuzumab	4 3 2 1	4 3 2 1
Results of a joint analysis of the IBCSG TEXT and SOFT trials: Adjuvant exemestane with ovarian function suppression versus tamoxifen with ovarian function suppression for premenopausal women with ER-positive early breast cancer	4 3 2 1	4 3 2 1
Ongoing Phase II feasibility study of dose-dense AC → eribulin as adjuvant therapy for early-stage HER2-negative breast cancer	4 3 2 1	4 3 2 1
Available research data (PALOMA-1) and ongoing Phase III investigation (PALOMA-2) with the CDK4/6 inhibitor palbociclib for ER-positive, HER2-negative 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 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
- Recall the recent FDA approval of neoadjuvant pertuzumab, and consider this therapeutic approach when evaluating appropriate patients with HER2-positive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Formulate individualized approaches to first- and later-line therapy for patients with HER2-negative metastatic breast cancer. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based algorithm for the initial and long-term treatment of localized hormone receptor-positive pre- and postmenopausal breast cancer. . . . . 4 3 2 1 N/M N/A
- Recognize the evolving application of biomarkers and multigene assays in breast cancer management, and effectively use these tools to refine or individualize treatment plans for patients. . . . . 4 3 2 1 N/M N/A

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

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Ann H Partridge, MD, MPH	4 3 2 1	4 3 2 1
Clifford Hudis, MD	4 3 2 1	4 3 2 1
John Crown, BCh, BAO, BSc, MD, MBA	4 3 2 1	4 3 2 1
Claudine Isaacs, 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:.....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

Street Address:..... Box/Suite:.....

City, State, Zip:.....

Telephone:..... Fax:.....

Email:.....

Research To Practice designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

The expiration date for this activity is October 2015. To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/BCU214/CME.

QID 1316

Breast Cancer®
UPDATE

Neil Love, MD
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

PRSRT STD
U.S. POSTAGE
PAID
MIAMI, FL
PERMIT #1317

This activity is supported by educational grants from
Eisai Inc, Genentech BioOncology, Genomic Health Inc
and Novartis Pharmaceuticals Corporation.

Research
To Practice®

Sponsored by Research To Practice.

Release date: October 2014
Expiration date: October 2015
Estimated time to complete: 3 hours

This program is printed on MacGregor XP paper, which is manufactured in accordance with the world's leading forest management certification standards.