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Breast Cancer® UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Sara M Tolaney, MD, MPH
Tiffany A Traina, MD
William J Gradishar, MD
Charles E Geyer Jr, MD

EDITOR

Neil Love, MD

CONTENTS

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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

- Establish an evidence-based algorithm for the treatment of hormone-sensitive advanced BC, including the use of endocrine, biologic and chemotherapeutic agents.
- Implement a long-term clinical plan for the management of metastatic HER2-positive BC, incorporating existing, recently approved and investigational targeted treatments.
- Recognize the evolving application of biomarkers and multigene assays in BC management, and effectively use these tools to refine or individualize treatment plans for patients.
- Formulate individualized approaches to first- and later-line therapy for patients with triple-negative BC.
- Develop an evidence-based algorithm for the initial and long-term treatment of localized hormone receptor-positive pre- and postmenopausal BC.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

3 **Sara M Tolaney, MD, MPH**
Department of Medical Oncology
Dana-Farber Cancer Institute
Instructor in Medicine
Harvard Medical School
Boston, Massachusetts

8 **Tiffany A Traina, MD**
Assistant Physician of the Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Assistant Professor of Medicine
Joan and Sanford I Weill Department of Medicine
Weill Cornell Medical College
New York, New York

11 **William J Gradishar, MD**
Betsy Bramsen Professor of Breast Oncology
Professor of Medicine; Director, Maggie Daley Center for Women's Cancer Care, Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Northwestern Memorial Hospital
Chicago, Illinois

14 **Charles E Geyer Jr, MD**
Associate Director
Clinical Trials Office
Massey Cancer Center
Richmond, Virginia

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

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INTERVIEW

Sara M Tolaney, MD, MPH

Dr Tolaney is Medical Oncologist in the Department of Medical Oncology at Dana-Farber Cancer Institute and Instructor in Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-14

Track 1 Efficacy of the CDK4/6 inhibitor palbociclib with letrozole as first-line or fulvestrant as second-line therapy for ER-positive, HER2-negative metastatic breast cancer (mBC)

Track 2 Tolerability of palbociclib

Track 3 Activity and tolerability of investigational CDK4/6 inhibitors — abemaciclib, ribociclib — for ER-positive mBC

Track 4 Incidence of palbociclib-associated neutropenia

Track 5 Sequencing of palbociclib-based therapy in ER-positive mBC

Track 6 **Case discussion:** A 58-year-old postmenopausal woman with de novo ER-positive, HER2-negative mBC with bone and lymph node metastases receives palbociclib and letrozole

Track 7 **Case discussion:** A 45-year-old woman with HER2-positive mBC receives pertuzumab/trastuzumab/paclitaxel

Track 8 Primary analysis of the Phase III ExteNET study: Neratinib after adjuvant chemotherapy with trastuzumab for HER2-positive early BC

Track 9 Activity and tolerability of T-DM1

Track 10 Clinical implications of the results from the MARIANNE study of T-DM1 with or without pertuzumab versus trastuzumab and a taxane as first-line therapy for HER2-positive mBC

Track 11 Counseling patients with mBC and young children

Track 12 **Case discussion:** A 55-year-old woman with a 1.2-cm, ER-negative, HER2-positive, node-negative invasive ductal carcinoma receives adjuvant paclitaxel/trastuzumab

Track 13 **Case discussion:** A 34-year-old woman with a family history of BC is diagnosed with high-grade triple-negative BC (TNBC) with a BRCA1 mutation

Track 14 Investigation of antibody-drug conjugates and immune checkpoint inhibitors in TNBC

Select Excerpts from the Interview

Tracks 1-5

DR LOVE: Palbociclib recently received accelerated approval for use as first-line therapy in combination with letrozole for postmenopausal women with ER-positive, HER2-negative metastatic breast cancer. Would you talk about its mechanism of action and efficacy?

DR TOLANEY: Palbociclib is a CDK4/6 inhibitor, and it works by causing cell cycle arrest that eventually leads to cellular apoptosis. CDK4/6 is thought to be an important target in ER-positive breast cancer because the cyclin D pathway drives a lot of these cancers. Preclinical data suggest that the addition of CDK4/6 inhibitors to hormonal therapy is synergistic.

PALOMA-1 was a Phase II study that randomly assigned patients to up-front letrozole alone or letrozole in combination with palbociclib. The results showed an impressive improvement in progression-free survival (PFS), from 10 to 20 months (Finn 2015; [1.1]). This led to the accelerated approval of palbociclib in combination with letrozole as first-line therapy for ER-positive metastatic breast cancer.

The Phase III PALOMA-3 trial recently presented at ASCO and published in *The New England Journal of Medicine* investigated palbociclib in combination with fulvestrant for women with ER-positive breast cancer who had experienced disease relapse. The results demonstrated an increase in PFS from 3.8 months to 9.2 months with the addition of palbociclib to fulvestrant (Turner 2015; [1.2]). These data suggest that palbociclib is also effective in the second-line setting. I believe that, based on these results, palbociclib will eventually receive full approval.

1.1

PALOMA-1: Results of a Phase II Study of Palbociclib with Letrozole versus Letrozole Alone as First-Line Treatment for Postmenopausal Women with ER-Positive, HER2-Negative Advanced Breast Cancer

Efficacy	Palbociclib + letrozole (n = 84)	Letrozole (n = 81)	Hazard ratio	*p*-value
Overall response rate	43%	33%	NR	0.13
Median PFS	20.2 mo	10.2 mo	0.488	0.0004
Median OS	37.5 mo	33.3 mo	0.813	0.42

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

Finn RS et al. *Lancet Oncol* 2015;16(1):25-35.

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* 2015;373(3):209-19; Turner NC et al. *Proc ASCO* 2015;**Abstract LBA502**.

These data will change how we treat ER-positive disease. Given the results of these studies, I would now consider administering fulvestrant in combination with palbociclib for patients with metastatic disease who experience disease progression on an adjuvant aromatase inhibitor. It is likely that CDK4/6 inhibition will provide added benefit irrespective of the type of hormonal therapy it is combined with.

DR LOVE: What are some of the typical side effects associated with palbociclib?

DR TOLANEY: Overall, palbociclib is fairly well tolerated. Neutropenia is the most significant toxicity. The data from both the PALOMA-1 and the PALOMA-3 study showed approximately a 60% rate of Grade 3 or 4 neutropenia. However, in both studies the rates of febrile neutropenia were not significant. Blood counts must be closely monitored. Neutropenia sometimes requires dose holds and reductions. Fatigue and mild nausea have also been reported.

DR LOVE: Would you review what is known about other CDK4/6 inhibitors and what strategies are currently under investigation with this class of agents?

DR TOLANEY: Three CDK4/6 inhibitors are currently under investigation — palbociclib, ribociclib and abemaciclib. In early studies, only abemaciclib has demonstrated a high monotherapy response rate. A Phase I study of abemaciclib in patients with ER-positive metastatic breast cancer demonstrated approximately a 25% monotherapy response, which is impressive (Patnaik 2014).

The Phase II MONARCH 1 study investigating abemaciclib monotherapy in patients with ER-positive metastatic breast cancer that has progressed on a minimum of 2 prior lines of chemotherapy and prior hormonal therapy recently completed accrual (NCT02102490). If that trial is positive, abemaciclib could be an exciting option for

1.3

Select Ongoing Phase III Trials Evaluating CDK4/6 Inhibitors for ER-Positive, HER2-Negative Breast Cancer

Trial identifiers	N	Disease setting	Treatment arms
MONARCH 3 (NCT02246621)	450	• Advanced disease, no prior systemic therapy • Postmenopausal	• Abemaciclib + NSAI • Placebo + NSAI
MONARCH 2 (NCT02107703)	630	• Advanced disease, ≤1 prior systemic therapy • Postmenopausal	• Abemaciclib + fulvestrant • Placebo + fulvestrant
PALLAS (NCT02513394)	4,600	• Early disease	• Palbociclib + standard ET • Standard ET
PENELOPE-B (NCT01864746)	1,100	• High-risk disease • After neoadjuvant chemotherapy	• Palbociclib + ET • Placebo + ET
MONALEESA-3 (NCT02422615)	660	• Advanced disease • Postmenopausal	• Ribociclib + fulvestrant • Placebo + fulvestrant
MONALEESA-7 (NCT02278120)	660	• Advanced disease • Premenopausal	• Ribociclib + NSAI/tamoxifen + goserelin • Placebo + NSAI/tamoxifen + goserelin

NSAI = nonsteroidal aromatase inhibitor; ET = endocrine therapy

www.clinicaltrials.gov. Accessed October 2015.

patients in that setting. Ongoing Phase III studies are evaluating abemaciclib with endocrine therapy in both the first- and second-line settings for ER-positive metastatic breast cancer (1.3). Abemaciclib has the added benefit of having CNS penetration, and studies are under way evaluating abemaciclib to treat brain metastases.

Tolerability differs among the CDK4/6 inhibitors. Abemaciclib is associated with lower rates of neutropenia than palbociclib, but it does cause higher rates of diarrhea.

Preclinical data also suggest that adding CDK4/6 inhibitors to either PI3 kinase or mTOR inhibitors may be synergistic. Studies with different triplet combinations are ongoing, including a trial evaluating the addition of ribociclib to exemestane and everolimus (NCT01857193). These triplet combinations are interesting, and we'll have to determine their toxicity profiles.

DR LOVE: Is this strategy being evaluated in the (neo)adjuvant setting?

DR TOLANEY: A Phase II randomized study is currently evaluating the safety of palbociclib in combination with endocrine therapy in the neoadjuvant setting for postmenopausal patients with ER-positive Stage II/III breast cancer (NCT02296801). The Phase III PALLAS trial is investigating the efficacy of palbociclib with adjuvant endocrine therapy for women with hormone receptor-positive breast cancer (1.3).

Track 8

DR LOVE: Moving to HER2-positive breast cancer, would you discuss the ExteNET study investigating the pan-HER tyrosine kinase inhibitor neratinib in early breast cancer?

DR TOLANEY: I enrolled several patients on this study randomly assigning women who had received trastuzumab-based adjuvant therapy to 1 year of neratinib or placebo. The study reported a small yet statistically significant benefit with the addition of neratinib,

1.4

ExteNET: Results of a Phase III Study of Neratinib After Adjuvant Therapy in HER2-Positive Early Breast Cancer

Efficacy	Neratinib (n = 1,420)	Placebo (n = 1,420)	Hazard ratio	*p*-value
IDFS (2 y)	93.9%	91.6%	0.67	0.009
DFS-DCIS (2 y)	93.9%	91.0%	0.63	0.002
Distant recurrence	3.7%	5.1%	NR	
	Neratinib (n = 1,408)		Placebo (n = 1,408)	
Select adverse events	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Diarrhea	95.4%	39.9%	35.4%	1.6%
Nausea	43.0%	1.8%	21.5%	0.1%
Fatigue	27.1%	1.6%	20.1%	0.4%

IDFS = invasive disease-free survival; DFS-DCIS = disease-free survival including occurrence of ductal carcinoma in situ; NR = not reported

Incidence of cardiac adverse events was similar in both arms.

Chan A et al. *Proc ASCO* 2015;**Abstract 508**.

but the follow-up is not long. A high rate of Grade 3 diarrhea was observed (Chan 2015; [1.4]). I had to dose reduce and hold the drug multiple times, and it does affect quality of life. I believe we need to determine which patients would benefit from this treatment if the longer-term follow-up data look good, because it does have considerable toxicity.

Track 10

DR LOVE: Would you talk about the Phase III MARIANNE study, which was presented at ASCO 2015?

DR TOLANEY: The MARIANNE trial was a 3-arm randomized trial that compared T-DM1 with or without pertuzumab to trastuzumab with a taxane as first-line therapy for HER2-positive metastatic breast cancer. Surprisingly, the 3 arms were not significantly different in terms of PFS (Ellis 2015; [1.5]).

Data from a Phase II trial by Sara Hurvitz comparing trastuzumab/docetaxel to T-DM1 as first-line therapy for metastatic breast cancer showed a significant increase in PFS with T-DM1 compared to the taxane/trastuzumab combination (Hurvitz 2013). So I anticipated that the addition of pertuzumab to T-DM1 would be effective. It is possible that results in different studies may vary with the patients enrolled. The other possibility is that T-DM1 is not as effective as the taxane/trastuzumab/pertuzumab combination. ■

1.5

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**.

SELECT PUBLICATIONS

Hurvitz S et al. **Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer.** *J Clin Oncol* 2013;31(9):1157-63.

Patnaik A et al. **LY2835219, a novel cell cycle inhibitor selective for CDK4/6, in combination with fulvestrant for patients with hormone receptor positive (HR+) metastatic breast cancer.** *Proc ASCO* 2014;**Abstract 534**.

INTERVIEW

Tiffany A Traina, MD

Dr Traina is Assistant Physician in the Breast Medicine Service at Memorial Sloan Kettering Cancer Center and Assistant Professor of Medicine in the Joan and Sanford I Weill Department of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-10

Track 1 Optimizing treatment strategies for TNBC based on heterogeneity among the distinct subtypes

Track 2 Results of a Phase II trial of the androgen receptor (AR) inhibitor enzalutamide in advanced AR-positive TNBC

Track 3 Ongoing investigations of enzalutamide-based therapy in ER-positive BC

Track 4 **Case discussion:** A 75-year-old woman with AR-positive TNBC experiences disease stabilization for 15 months with enzalutamide on a clinical trial

Track 5 Activity and side-effect profile of eribulin in patients with TNBC

Track 6 Advantages of nanoparticle albumin-bound (*nab*) paclitaxel versus solvent-based paclitaxel for patients with TNBC

Track 7 Approach to genetic counseling for patients with TNBC

Track 8 Use of next-generation sequencing in patients with TNBC

Track 9 Promising activity of the PARP inhibitor veliparib in TNBC

Track 10 Clinical use of a scalp hypothermia system to prevent chemotherapy-induced alopecia

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss the efficacy and tolerability observed with enzalutamide in your Phase II trial for patients with advanced androgen receptor (AR)-positive triple-negative breast cancer (TNBC) (Traina 2015; [2.1])?

DR TRAINA: TNBC accounts for about 20% of all breast cancer. Based on the enzalutamide prospective screening, as many as 55% of triple-negative cases had some degree of AR expression. In this study, we observed the first RECIST-confirmed responses elicited by an antiandrogen in TNBC, including a patient with a complete response. Such responses were not observed with bicalutamide in the Phase II TBCRC 011 trial (Gucalp 2013).

We also observed radiographic responses with symptom improvement and resolution of pleural effusions, and the duration of response was quite long. In the trial, the primary endpoint was clinical benefit rate (CBR) at ≥16 weeks, which was 35%. CBR at 24 weeks was also determined, and this was 29%. This suggests that patients are able to have at least stable disease for 6 months with a simple daily oral endocrine option, which in comparison to standard cytotoxics, such as taxanes or platinums, enzalutamide is extremely well tolerated.

In terms of side effects, fatigue was noted on the Phase II trial but not to a large degree. Compared to what has been observed in the prostate cancer setting, use of enzalutamide was not associated with any seizure activity. Some patients experienced a bit of fogginess or cognitive slowdown, but these were simply managed by switching the administration of the drug from morning to evening.

Separate from TNBC, we see high coexpression of AR with estrogen receptor. In ER-positive breast cancer, it's as high as 80% coexpression. As resistance to estrogen-targeted therapies develops, dependence on AR signaling increases, so antiandrogens may have a role in breast cancers that are resistant to antiestrogen therapy. That's one area of interest now in clinical trials.

A Phase II trial of enzalutamide and exemestane in patients with estrogen or progesterone receptor-positive breast cancer is ongoing (NCT02007512). Patients are randomly assigned to receive exemestane in combination with enzalutamide or placebo. We anticipate a report of at least some of the results from that trial this year.

Because ER-positive breast cancer has a luminal-type profile, we believe that mechanisms of resistance involving enzymes such as PI3 kinase or CDK might play a role. A multicenter Phase I/II trial of enzalutamide with or without the PI3 kinase inhibitor taselisib for patients with AR-positive metastatic TNBC is ongoing (NCT02457910). A small Phase II trial by Memorial Sloan Kettering Cancer Center to investigate an AR antagonist in combination with palbociclib is also planned.

2.1

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.

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

Track 5

DR LOVE: What are your thoughts on the results of the Phase III Study 301 trial of eribulin versus capecitabine for patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes (Kaufman 2012, 2015)?

DR TRAINA: In the overall study population, both agents yielded equivalent efficacy. However, in the subset population of patients with TNBC, a trend was evident in favor of eribulin compared to capecitabine. Eribulin is well tolerated. The main side effects are neutropenia and neuropathy. Although the earlier Phase III EMBRACE trial compared eribulin to treatment of physician's choice, that study had no statistical power or ability to compare eribulin to each chosen agent (Cortes 2011).

In my practice, I see less of a problem with neutropenia in earlier lines of therapy. We're able to manage neutropenia with dose reductions and with growth factor support. Eribulin is a reasonable option, but I am uncertain how it compares to paclitaxel as first-line therapy in terms of efficacy.

Track 10

DR LOVE: Can you discuss the results of the prospective trial of the scalp hypothermia system for preventing chemotherapy-induced alopecia in women with Stage I to Stage II breast cancer that were presented at ASCO 2015 (Rugo 2015)?

DR TRAINA: Those results are inspiring, suggesting that the use of the scalp hypothermia system when administering certain (neo)adjuvant chemotherapy regimens, excluding taxanes and anthracyclines, could result in a success rate of approximately 70% in alleviating alopecia to a degree such that women would not require a wig. The downside is that these hypothermal caps are quite laborious and challenging to wear. One of the systems that we've used requires multiple caps. The burden is largely on the patient to bring dry ice in coolers or employ professional "cappers." For those for whom alopecia is a real obstacle, I believe it's a reasonable preventive measure.

The results of this study have been practice changing. We give patients written educational materials about this option and have the resources available so that, if a patient would like to pursue the cold cap strategy, we have the mechanism in place. ■

SELECT PUBLICATIONS

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

Gucalp A et al. **Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer.** *Clin Cancer Res* 2013;19(19):5505-12.

Kaufman PA et al. **Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane.** *J Clin Oncol* 2015;33(6):594-601.

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

Rugo HS et al. **Clinical performance of the DigniCap system, a scalp hypothermia system, in preventing chemotherapy-induced alopecia.** *Proc ASCO* 2015;**Abstract 9518**.

Rugo HS et al. **Use of the DigniCap system to prevent hair loss in women receiving chemotherapy (CTX) for Stage I breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract P2-12-11**.

INTERVIEW

William J Gradishar, MD

Dr Gradishar is Betsy Bramsen Professor of Breast Oncology, Professor of Medicine and Director of the Maggie Daley Center for Women's Cancer Care at the Northwestern University Feinberg School of Medicine's Robert H Lurie Comprehensive Cancer Center in Chicago, Illinois.

Tracks 1-10

Track 1 **Case discussion:** A 60-year-old woman with Stage I, ER-positive, HER2-negative BC initially treated with adjuvant anastrozole presents with an asymptomatic liver metastasis

Track 2 Viewpoint on the results of the Phase III PALOMA-3 trial: Fulvestrant with or without palbociclib in ER-positive, HER2-negative mBC after disease progression on prior endocrine therapy

Track 3 **Case discussion:** A 65-year-old woman with ER-positive mBC receives everolimus/exemestane

Track 4 Management of everolimus-associated mucositis

Track 5 **Case discussion:** A 42-year-old woman with newly diagnosed TNBC experiences a near-complete response to neoadjuvant eribulin/carboplatin on a clinical trial

Track 6 Impact of HER2 and estrogen receptor status on decisions regarding the use of neoadjuvant chemotherapy

Track 7 Perspective of NCCN Breast Committee Chair on the use of (neo)adjuvant pertuzumab

Track 8 **Case discussion:** A 42-year-old woman with a 2.8-cm, ER-positive, HER2-negative BC, a negative sentinel node and an Onco*type* DX® 21-gene Recurrence Score® of 8

Track 9 Application of Onco*type* DX in early-stage, node-positive BC

Track 10 Results of the Phase III Intergroup S0307 study of bisphosphonates as adjuvant therapy for primary BC

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you comment on your clinical experience with palbociclib?

DR GRADISHAR: The data with palbociclib are impressive (1.1, 1.2; page 4), and my experience has been that patients receiving palbociclib don't notice much in terms of side effects. Where the quality of life changes — and I say this somewhat tongue in cheek — is for the physician because rather than administering endocrine therapy and saying, "See you in 3 months," we're saying, "You're receiving palbociclib. You need to come back in 1 month." So we have to be more vigilant about monitoring blood counts regularly.

Neutropenic fevers have been uncommon. Patients do develop asymptomatic neutropenia, but we haven't had to hospitalize anyone. We haven't documented any infections, but for a fair number of patients we've held or reduced the dose. Most of our patients, if not all, have tolerated palbociclib well.

DR LOVE: We are accustomed to sequencing endocrine therapies. Would it make sense to continue the CDK inhibitor and switch the endocrine therapy?

DR GRADISHAR: That's a question I hope we'll address in the future. Trials are evaluating continuing everolimus and switching endocrine therapy. We don't have any data yet, but a similar argument could be made for palbociclib. Using it continuously could be reasonable, but at this time we stop.

I believe with time more patients will receive palbociclib up front and everolimus will be pushed back simply on the basis of tolerability. Patients experience more problems with everolimus. Some have clearly benefited from the combination with hormone therapy, but they can develop mouth sores, peripheral edema and pneumonitis. In many cases we reduce the dose of everolimus from 10 mg to 5 mg to be able to continue therapy. We use the corticosteroid mouthwashes, and they help minimize the symptoms of the mouth sores.

DR LOVE: Do you envision combining adjuvant endocrine therapy with a CDK inhibitor in the future?

DR GRADISHAR: Trials are under way. Another important question is, are we always obligated to use dual therapy? I believe a case can be made for endocrine monotherapy for certain patients with indolent disease.

Track 7

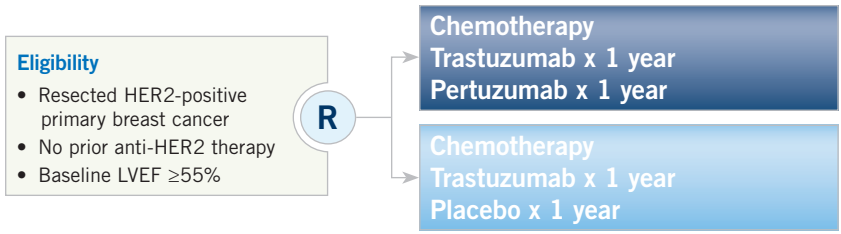
DR LOVE: As chair of the NCCN Breast Cancer Guidelines Panel, would you discuss the debate regarding the use of adjuvant pertuzumab and how it has affected your practice?

DR GRADISHAR: The debate centered on the fact that pertuzumab was FDA approved for use preoperatively within certain criteria — tumors larger than 2 centimeters or with positive nodes. So we had a license to use it in that setting, but in the adjuvant setting we're lacking the data that will come from the APHINITY trial, evaluating pertuzumab-based adjuvant therapy (3.1).

3.1

APHINITY: A Phase III Trial of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy for Patients with HER2-Positive Primary Breast Cancer

Protocol ID: NCT01358877 **Enrollment:** 4,805



LVEF = left ventricular ejection fraction

Primary endpoint: Invasive disease-free survival

www.clinicaltrials.gov. Accessed October 2015.

However, the group believes that if you see a patient postoperatively who would have been a candidate for preoperative pertuzumab, that patient should have the same opportunity to receive the agent after surgery. The language is purposely a little vague about the duration, but we did suggest in the NCCN guidelines that it would be reasonable to administer pertuzumab postoperatively. If you elected to do that, you could administer it for a similar duration to what you would use preoperatively.

I have personally administered adjuvant pertuzumab to a couple of my patients. However, both were prepared to pay for the treatment themselves and are now doing so. But I am not overly eager to administer it for a full year, at least until we have data from the APHINITY study.

Track 10

DR LOVE: Would you discuss the results of the long-awaited SWOG-S0307 study of bisphosphonates as adjuvant therapy for primary breast cancer (Gralow 2015)?

DR GRADISHAR: This was a trial of 3 different bone-targeted agents — zoledronic acid, ibandronate and clodronate. All of the efficacy parameters were perfectly superimposable. No difference was observed among the 3 arms.

The toxicity was also comparable. The incidence of osteonecrosis of the jaw was slightly higher among patients who received zoledronic acid, but the difference was about half a percentage point. So I don't want to say the trial was a "wash," but it didn't tell us that one agent is better. A majority of patients who participated in the trial indicated a preference for oral bisphosphonate formulations. The author concluded that these oral agents should therefore be made available in the United States.

DR LOVE: The hope was that using zoledronic acid would result in less disease recurrence. Do you believe these results negate that idea?

DR GRADISHAR: That effect would be difficult to identify in this trial. Some advocates believe that bisphosphonates can affect disease recurrence in breast cancer, but it's debatable. I have not seen any data that address the issue definitively. ■

SELECT PUBLICATIONS

A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer. NCT01358877

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Adjuvant bisphosphonate treatment in early breast cancer: Meta-analyses of individual patient data from randomised trials.** *Lancet* 2015;386(10001):1353-61.

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.

Gralow J et al. **Phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials Group/NRG Oncology study S0307.** *Proc ASCO* 2015;**Abstract 503**.

Turner NC et al. **Palbociclib in hormone-receptor–positive advanced breast cancer.** *N Engl J Med* 2015;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* 2015;**Abstract LBA502**.

INTERVIEW

Charles E Geyer Jr, MD

Dr Geyer is Associate Director of the Clinical Trials Office at Massey Cancer Center in Richmond, Virginia.

Tracks 1-11

Track 1 OlympiA: A Phase III trial of adjuvant olaparib in patients with high-risk HER2-negative BC and a germline BRCA1/2 mutation

Track 2 Indications for BRCA germline testing

Track 3 Monitoring and management of olaparib-associated adverse events on a clinical trial

Track 4 Viewpoint on the risk of secondary leukemias with olaparib

Track 5 Activity and ongoing investigation of veliparib-based therapy in mBC

Track 6 Comparison of olaparib and veliparib

Track 7 Potential integration of olaparib into the therapeutic algorithm for BC

Track 8 Personal use of genomic assays — Onco*type* DX, Prosigna® and the Breast Cancer Index℠

Track 9 GeparSepto GBG 69: Results of a Phase III trial comparing neoadjuvant weekly *nab* paclitaxel to solvent-based paclitaxel → anthracycline/cyclophosphamide for early BC

Track 10 *Nab* paclitaxel for metastatic TNBC

Track 11 Primary results of the NSABP-B-35 trial of anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy and radiation therapy

Select Excerpts from the Interview

Tracks 1-2, 5

DR LOVE: Could you review some of the ongoing trial concepts evaluating PARP inhibitors in the management of BRCA-mutated HER2-negative breast cancer?

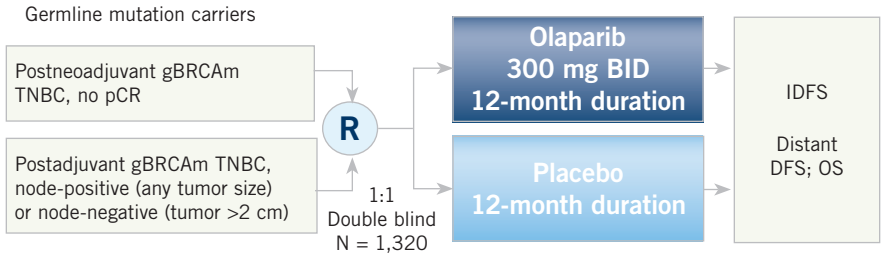
DR GEYER: Studies have demonstrated that with the monotherapy PARP inhibitor approach, the presence of germline BRCA mutation underlying the breast cancer is necessary for good activity to be observed. In a Phase II study of 2 dose levels of olaparib for women with confirmed BRCA1- or BRCA2-mutant, advanced, heavily pretreated breast cancer, the objective response rate was 41% (Tutt 2010).

PARP inhibitors have also been evaluated as monotherapy for patients with TNBC with or without germline BRCA mutations. An interesting study that I am involved with called the OlympiA trial is currently evaluating adjuvant olaparib monotherapy (Tutt 2015; [4.1]).

The eligibility criteria for this study are broad. Patients with germline BRCA1 or BRCA2 mutations who have completed definitive local treatment and at least 6 cycles of neoadjuvant or adjuvant chemotherapy are eligible. Patients with TNBC must have node-positive disease or node-negative disease with tumors larger than 2 centimeters.

4.1

OlympiA: A Phase III Trial of Olaparib as Adjuvant Therapy for Germline BRCA-Mutated (gBRCAm), High-Risk HER2-Negative Primary Breast Cancer



TNBC = triple-negative breast cancer; pCR = pathologic complete response; IDFS = invasive disease-free survival; OS = overall survival

Tutt A et al. *Proc ASCO* 2015;**Abstract TPS1109**.

If they have received neoadjuvant chemotherapy, they must have residual disease in the breast or lymph nodes. Patients with ER-positive disease in the adjuvant setting should have 4 or more positive nodes, making the disease high risk in nature.

Other studies are investigating augmenting the activity of DNA-targeting agents, such as carboplatin, by adding a PARP inhibitor (NCT02163694) for patients with locally advanced or metastatic disease.

Another study the NSABP is participating in is the Phase III neoadjuvant BRIGHTNESS study of veliparib and carboplatin/paclitaxel in TNBC (NCT02032277). The study was launched after the results of the Phase II I-SPY 2 trial demonstrated a jump in pathologic complete response rate from 26% in the control arm to 52% in the veliparib/carboplatin/paclitaxel arm for patients with hormone receptor–negative and HER2-negative breast cancer and a 90% probability of success in a Phase III trial (Rugo 2013).

Track 8

DR LOVE: What is your approach to the use of genomic testing in the adjuvant ER-positive, HER2-negative setting? Which assays, if any, do you use, and in what situations?

DR GEYER: I routinely use the Onco*type* DX assay for patients with node-negative disease who have T1c tumors. I tend not to order it for clear high-grade cancer because I have found that in that situation I usually wind up treating the cancer anyway. I have started using the Onco*type* DX assay occasionally for patients with larger tumors in the neoadjuvant setting. In my opinion the Onco*type* DX assay is the best test we have to determine whether chemotherapy can benefit the patient.

DR LOVE: Have you used any of these assays to help make a decision whether to extend or end endocrine therapy at 5 years?

DR GEYER: For patients with node-positive disease I tend to continue therapy. And if the patient is experiencing a lot of side effects, that usually drives the duration of

therapy. But I do use genomic testing when the additional information will help the patient and me to determine the best next step in terms of therapy.

I find the data on the Breast Cancer Index interesting in this setting (Sgroi 2013; [4.2]). That's the assay that I'm ordering right now if I'm considering stopping endocrine therapy at 5 years, but I want something to support that.

4.2

Prediction of Late Distant Recurrence (DR) in Patients with ER-Positive, Node-Negative Breast Cancer Using the Breast Cancer Index (BCI)

BCI linear (BCI-L) model	10-year DR	Hazard ratio (adjusted for CTS*)
BCI-L low (n = 390)	4.8%	Reference
BCI-L intermediate (n = 166)	18.3%	2.89
BCI-L high (n = 109)	29.0%	4.86

* Clinical Treatment Scores (CTS) is a prognostic model using the classical variables of tumor size and grade, lymph node status, age and treatment.

Conclusion: The 3 BCI-L groups identified 2 risk populations for both early and late DR with 84% (556/665) of patients having a low risk for early DR and a smaller population (39%, 230/596) having a high risk for late DR who may benefit from extended endocrine or other therapy.

Sgroi DC et al. *Lancet Oncol* 2013;14(11):1067-76.

Tracks 9-10

DR LOVE: Would you discuss the results of the Phase III GeparSepto (GBG 69) trial comparing neoadjuvant *nab* paclitaxel to solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (Untch 2014; [4.3])?

DR GEYER: In the final study design, patients received solvent-based paclitaxel at 80 mg/m^2 or *nab* paclitaxel at the reduced dose of 125 mg/m^2. The pathologic complete response rate was 38% with *nab* paclitaxel compared to 29% with solvent-based paclitaxel. The study does raise the question whether these results can translate into a difference in disease-free or overall survival.

I'm a fan of using *nab* paclitaxel. I like to avoid steroid premedication. For a patient with preexisting diabetes, I find *nab* paclitaxel a much easier agent to administer. My own experience and my personal bias is that at the lesser dose of 125 mg/m^2 it doesn't seem to cause neuropathy, which I believe is a serious problem in the adjuvant setting. I'm not sure whether at the higher dose it causes as much neuropathy as solvent-based paclitaxel does.

Track 11

DR LOVE: What are your thoughts on the results of the Phase III NSABP-B-35 trial of tamoxifen versus anastrozole for postmenopausal patients with ductal carcinoma in situ (Margolese 2015)?

DR GEYER: It's not often you see an initial presentation with a median follow-up of 9 years. The primary endpoint was breast cancer-free interval (BCFI), which was partly why the study took so long.

4.3

GeparSepto (GBG 69): Efficacy and Safety Results from the Phase III Trial of Neoadjuvant Chemotherapy with Nanoparticle-Based Paclitaxel (*nab*-P) versus Solvent-Based Paclitaxel (sb-P), Administered Weekly and Followed by Anthracycline/Cyclophosphamide for Patients with Early Breast Cancer

Primary endpoint	**sb-P** (n = 598)	***nab*-P** (n = 606)	Odds ratio	*p*-value
pCR (ypT0 ypN0)	29%	38%	1.5	0.001

Grade 3 or 4 AEs	**sb-P** (n = 598)	***nab*-P** (n = 606)	*p*-value
Neutropenia	61.8%	60.5%	0.636
Fatigue	4.7%	5.9%	0.369
Diarrhea	2.8%	3.3%	0.739
Peripheral sensory neuropathy*	2.7%	10.2%	<0.001
Anemia	1.0%	2.5%	0.076
Hand-foot syndrome	1.0%	2.3%	0.112

pCR = pathologic complete response; AE = adverse event

* Grade 3-4 peripheral sensory neuropathy with *nab*-P 125 mg/m^2: 6 (5.5%)

Four deaths occurred on the study: sb-P, n = 1 due to cardiac decompensation; *nab*-P, n = 3 due to accident at home, multiorgan failure and sepsis.

Conclusion: GeparSepto showed that the pCR rate is significantly higher with *nab*-P than with sb-P when administered weekly before anthracycline-based chemotherapy.

Untch M et al. San Antonio Breast Cancer Symposium 2014;**Abstract PD2-6**.

The Kaplan-Meier curves for BCFI did not show any divergence until about 5 years, with fewer breast cancer recurrences in the anastrozole arm than in the tamoxifen arm. Even though the absolute differences were not great, the hazard ratio was 0.73 and the difference in 10-year BCFI rate was statistically significant with 89.2% for tamoxifen and 93.5% for anastrozole. Interestingly, when the results were broken down by age (younger than 60 versus 60 years or older) the treatment-by-age interaction was statistically significant, suggesting that women younger than age 60 benefitted more from anastrozole compared to tamoxifen. ■

SELECT PUBLICATIONS

Augustovski F et al. **Decision-making impact on adjuvant chemotherapy allocation in early node-negative breast cancer with a 21-gene assay: Systematic review and meta-analysis.** *Breast Cancer Res Treat* 2015;152(3):611-25.

Margolese RG et al. **Primary results, NRG Oncology/NSABP B-35: A clinical trial of anastrozole (A) versus tamoxifen (tam) in postmenopausal patients with DCIS undergoing lumpectomy plus radiotherapy.** *Proc ASCO* 2015;**Abstract LBA500**.

Rugo HS et al. **Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 trial.** San Antonio Breast Cancer Symposium 2013;**Abstract S5-02**.

Tutt A et al. **Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial.** *Lancet* 2010;376(9737):235-44.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The most common Grade 3 or 4 adverse event in the PALOMA-3 study evaluating the addition of palbociclib to fulvestrant for ER-positive, HER2-negative advanced breast cancer was _____.**
   a. Neutropenia
   b. Thrombocytopenia
   c. Diarrhea

2. **Which of the following CDK4/6 inhibitors has demonstrated significant monotherapy response rates among patients with hormone receptor-positive metastatic breast cancer?**
   a. Abemaciclib
   b. Palbociclib
   c. Ribociclib

3. **The Phase III ExteNET trial, which investigated neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer, reported a significant improvement in _____ on the neratinib arm.**
   a. Invasive disease-free survival (DFS)
   b. DFS including occurrence of DCIS
   c. Both a and b

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

5. **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. Enzalutamide demonstrated a CBR at 16 weeks of 39% in patients with AR-positive TNBC
   b. Enzalutamide did not demonstrate any clinical benefit in patients with AR-positive TNBC
   c. Enzalutamide induced Grade 3 or higher fatigue in 5% of the overall patient population
   d. As in prostate cancer, enzalutamide was associated with seizures in the overall patient population
   e. Both a and c
   f. Both b and d

6. **The results of a prospective trial of the scalp hypothermia system reported the technique to be highly effective with a success rate of approximately 70% in reducing chemotherapy-induced alopecia in women with Stage I/II breast cancer receiving nonanthracycline-based neoadjuvant or adjuvant chemotherapy regimens.**
   a. True
   b. False

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

8. **The SWOG-S0307 trial of zoledronic acid versus ibandronate versus clodronate did not result in a significant difference among the 3 arms in terms of efficacy.**
   a. True
   b. False

9. **The ongoing Phase III OlympiA trial is investigating therapy with single-agent _____ versus placebo for patients with germline BRCA-mutant, high-risk HER2-negative primary breast cancer.**
   a. Olaparib
   b. Veliparib
   c. Talazoparib
   d. Cediranib

10. **The results of the Phase III GeparSepto (GBG 69) trial evaluating neoadjuvant chemotherapy with weekly *nab* paclitaxel versus solvent-based paclitaxel, followed by anthracycline and cyclophosphamide, for patients with early-stage breast cancer yielded a statistically significant improvement in _____ with *nab* paclitaxel.**
    a. Pathologic complete response rate
    b. Rate of neutropenia
    c. Rate of anemia
    d. Both a and b
    e. All of the above
    f. None of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 1, 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
Clinical implications of the PALOMA-3 trial of fulvestrant with or without palbociclib for pre- and postmenopausal women with ER/PR-positive, HER2-negative metastatic breast cancer	4 3 2 1	4 3 2 1
Results of a Phase II trial of the AR inhibitor enzalutamide in advanced AR-positive TNBC	4 3 2 1	4 3 2 1
Clinical implications of the results of the MARIANNE study of T-DM1 with or without pertuzumab versus trastuzumab with a taxane as first-line therapy for HER2-positive metastatic breast cancer	4 3 2 1	4 3 2 1
GeparSepto GBG 69: Rates of pathologic complete response on a Phase III trial of neoadjuvant *nab* paclitaxel versus solvent-based paclitaxel for patients with early breast cancer	4 3 2 1	4 3 2 1
Improvement in DFS and BCFI in postmenopausal women younger than 60 years with DCIS receiving anastrozole versus tamoxifen on the NSABP-B-35 trial	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:

- Establish an evidence-based algorithm for the treatment of hormone-sensitive advanced BC, including the use of endocrine, biologic and chemotherapeutic 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
- Recognize the evolving application of biomarkers and multigene assays in BC management, and effectively use these tools to refine or individualize treatment plans for patients.....4 3 2 1 N/M N/A
- Formulate individualized approaches to first- and later-line therapy for patients with triple-negative BC.....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 BC.....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			
Sara M Tolaney, MD, MPH	4	3	2	1	4	3	2	1
Tiffany A Traina, MD	4	3	2	1	4	3	2	1
William J Gradishar, MD	4	3	2	1	4	3	2	1
Charles E Geyer Jr, 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:

.....

.....

.....

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