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Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Sandra M Swain, MD
Professor Alan Ashworth, FRS
Michael Untch, MD, PhD
Luca Gianni, MD
Nicholas J Robert, MD

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CME Certified

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Breast Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Results from numerous ongoing clinical trials lead to the continual emergence of new therapeutic agents, treatment strategies and diagnostic, prognostic and even predictive tools. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Determine the utility of genomic assays for counseling patients with ER-positive early breast cancer about their risk of recurrence and the potential benefits of adjuvant chemotherapy.
- Develop evidence-based treatment approaches for patients with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Evaluate the unique mechanisms of action and emerging clinical data for novel anti-HER2 agents under investigation in breast cancer.
- Appraise the risks and benefits of bevacizumab-based therapy for patients with HER2-negative metastatic breast cancer.
- Summarize the presumed mechanism of action of PARP inhibitors in breast cancer, particularly in patients with BRCA1/2 mutations and/or triple-negative disease.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

3 **Sandra M Swain, MD**
Medical Director, Washington Cancer Institute
Washington Hospital Center
Professor of Medicine, Georgetown University
Washington, DC

6 **Professor Alan Ashworth, FRS**
Director, Breakthrough Breast Cancer Research Centre
The Institute of Cancer Research
London, United Kingdom

9 **Michael Untch, MD, PhD**
Head of the Clinic for Gynecology
Gynecologic Oncology and Obstetrics
Head of the Breast Cancer Center
HELIOS Klinikum Berlin-Buch
Academic Hospital of the University Charité
Berlin, Germany

12 **Luca Gianni, MD**
Director of Medical Oncology 1
Department of Medical Oncology
Istituto Nazionale Tumori di Milano
Milan, Italy

15 **Nicholas J Robert, MD**
Associate Chair, Breast Cancer Committee, US Oncology Research Network
Chairman, Cancer Committee, Cancer Center, Inova Fairfax Hospital
Virginia Cancer Specialists
Fairfax, Virginia

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

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INTERVIEW

Sandra M Swain, MD

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

Tracks 1-21

Track 1 AZURE trial: Adjuvant zoledronic acid in early breast cancer (BC)

Track 2 Neoadjuvant trials of chemotherapy/anti-HER2 therapy for patients with HER2-positive early BC

Track 3 Lapatinib-associated diarrhea

Track 4 Selection of anti-HER2 therapy for patients with HER2-positive metastatic BC

Track 5 Mechanism of action of pertuzumab

Track 6 Neoadjuvant studies in operable HER2-positive BC

Track 7 Choice of adjuvant chemotherapy for HER2-positive, node-positive BC

Track 8 Neoadjuvant and adjuvant studies of pertuzumab for HER2-positive BC

Track 9 Rationale for and activity of bevacizumab combined with trastuzumab in HER2-positive BC

Track 10 Upcoming NSABP trials for HER2-positive early BC

Track 11 Activity of T-DM1 in heavily pretreated, HER2-positive metastatic BC

Track 12 Perspective on the use of bevacizumab in metastatic BC

Track 13 PARP inhibitors and BRCA testing in triple-negative BC (TNBC)

Track 14 Microtubule stabilizing agents in BC

Track 15 NCCTG-N9831 and BCIRG 005/006 studies: Round-robin review of HER2 testing in the context of adjuvant therapy for BC

Track 16 Results of clinical trials incorporating capecitabine into the adjuvant treatment of early BC

Track 17 Role of Onco*type* DX® for younger patients with ER-positive BC

Track 18 RSPC — Recurrence Score-Pathology-Clinical as an additional prognostic factor

Track 19 Use of Onco*type* DX in patients with node-positive tumors

Track 20 500-mg monthly fulvestrant dosing in ER-positive metastatic BC

Track 21 Neoadjuvant aromatase inhibitors in ER-positive BC

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts about the AZURE trial results evaluating adjuvant zoledronic acid?

DR SWAIN: I have spoken to many younger patients about whether or not they should receive adjuvant bisphosphonates because of the prior Austrian study results (Gnant 2009). So the AZURE trial data were important because it was clearly a negative study (Coleman 2010). I don't buy into the subset analysis that showed a benefit in postmenopausal women.

The NSABP trial with adjuvant clodronate has not yet been reported, and that study could be a tiebreaker. However, I believe it is now clear that the routine use of adjuvant bisphosphonates is not a standard treatment.

Track 17

DR LOVE: What are your thoughts on the role of Onco*type* DX for younger patients?

DR SWAIN: Breast cancer in younger women is usually correlated with an increased risk of recurrence and decreased survival compared to older patients.

In view of this, many clinicians are concerned about making treatment decisions on the basis of the Onco*type* DX assay and not administering adjuvant chemotherapy to patients with breast cancer who are younger than age 40 if the Recurrence Score® (RS) is low.

We recently presented our findings at San Antonio from more than 5,000 women younger than age 40 in whom we found results similar to the rest of the breast cancer population. The only difference we found was that younger patients tended to have a higher proportion of tumors with high RS (Shak 2010; [1.1]).

I find these data interesting, and I hope they will convince clinicians that Onco*type* DX is a useful test in this group also.

1.1

Recurrence Score (RS) in a Large Cohort of Patients in Three Separate Age Groups

		RS group		
Patient age (in years) (n)	Median RS	RS < 18	RS 18-30	RS ≥ 31
≤40 (5,794)	18.8	45.7%	39.4%	14.9%
41-69 (117,744)	17.0	55.4%	35.0%	9.6%
≥70 (21,702)	16.7	56.1%	33.5%	10.4%
All patients (145,240)	17.0	55.1%	35.0%	9.9%

"A wide range of RS was observed across all age groups. Many younger patients have low-RS disease, and many older patients have high-RS disease. These data also indicate that, for ER-positive breast cancer, age does not predict individual tumor biology."

Shak S et al. San Antonio Breast Cancer Symposium 2010;**Abstract P3-10-01**.

Track 18

DR LOVE: What are your thoughts on the Recurrence Score-Pathology-Clinical (RSPC), reported by your group, the NSABP, and developed as an integration of RS and clinicopathologic factors, including age, tumor size or tumor grade, in node-negative, ER-positive breast cancer?

DR SWAIN: Physicians use clinicopathologic features all the time in everyday practice. The goal of the RSPC is to objectively refine that information, especially for a patient with an intermediate RS.

What has been shown is that RSPC downgrades approximately 10 percent of cases from intermediate risk to low risk, but the final conclusions are that RS used alone remains the best predictor of chemotherapy benefit in ER-positive, node-negative breast cancer and the interaction of RSPC with treatment is not significant, although the trend was in the same direction as RS (Tang 2010).

Track 19

DR LOVE: Where are we in terms of evaluating RS in patients with node-positive breast cancer?

DR SWAIN: SWOG is planning a prospective study, SWOG-S1007, which will evaluate Onco*type* DX in patients with ER-positive, node-positive breast cancer. The study will randomly assign patients with an RS less than 25 to either receive chemotherapy or not. I believe it is the correct study to conduct, but it might make some physicians nervous when randomly assigning patients with positive nodes to receive or not receive adjuvant chemotherapy because there is an overall risk of recurrence of approximately 40 percent, even in patients with a low RS. ■

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Coleman RE et al. **Adjuvant treatment with zoledronic acid in Stage II/III breast cancer. The AZURE trial (BIG 01/04).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-5**.

Eng-Wong J et al. **Prediction of benefit from adjuvant treatment in patients with breast cancer.** *Clin Breast Cancer* 2010;10(Suppl 1):E32-7.

Gnant M et al. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91.

Kelly CM et al. **Utility of Onco*type* DX risk estimates in clinically intermediate risk hormone receptor-positive, HER2-normal, grade II, lymph node-negative breast cancers.** *Cancer* 2010;116(22):5161-7.

Shak S et al. **Quantitative gene expression analysis in a large cohort of estrogen-receptor positive breast cancers: Characterization of the tumor profiles in younger patients (≤40 yrs) and in older patients (≥70 yrs).** San Antonio Breast Cancer Symposium 2010;**Abstract P3-10-01**.

Tang G et al. **Comparing the prediction of chemotherapy benefit in patients with node-negative, ER-positive breast cancer using the recurrence score and a new measure that integrates clinical and pathologic factors with the recurrence score.** San Antonio Breast Cancer Symposium 2010;**Abstract S4-9**.

INTERVIEW

Professor Alan Ashworth, FRS

Prof Ashworth is Director of the Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research in London, United Kingdom.

Tracks 1-6

Track 1	Identification of the BRCA2 gene in BC	Track 4	Synthetic lethality and exploiting genetic defects in cancer
Track 2	BRCA mutations and mechanisms of DNA repair	Track 5	Potential predictive biomarkers for PARP inhibitors
Track 3	Preclinical and clinical development of PARP inhibitors	Track 6	Concepts of "oncogene addiction" versus "synthetic lethality"

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Would you outline the development of PARP inhibitors and the concept of synthetic lethality?

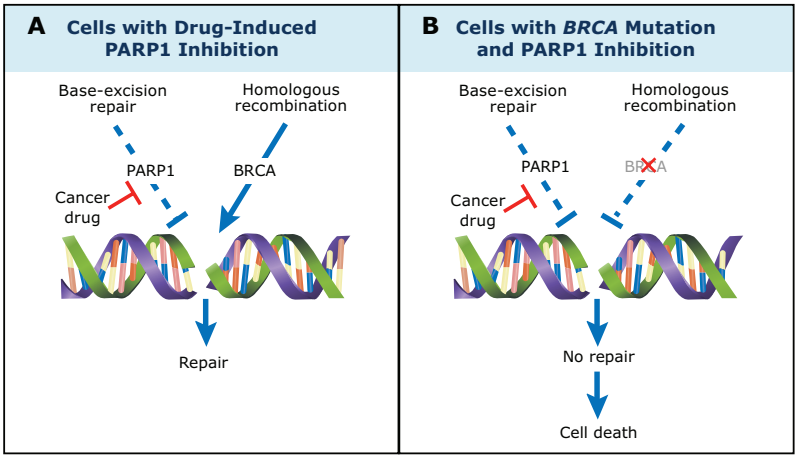
PROF ASHWORTH: The PARP enzyme was discovered in the early 1960s, and PARP inhibitors have been around for approximately 20 years. The early PARP inhibitors were not potent or specific. However, the recent agents in this class have proven to be active in inhibiting the PARP enzyme.

The idea of using PARP inhibitors is to induce synthetic lethality in BRCA-mutant cells by damaging the DNA with chemotherapy and then inhibiting the PARP to prevent repair (Iglehart 2009; [2.1]).

Imagine two separate defects in biochemical pathways not having any ostensible effects by themselves, but if the two defects are put together, then we have a combination or "synthesis" of lethalities. The two pathways act in a semiredundant fashion, and one takes over when the other has a malfunction. If both pathways are inhibited, then the system collapses.

The Phase I and II clinical trials of olaparib established the proof of concept of synthetic lethality in vivo (Tutt 2010). The other clinically evaluated PARP inhibitor, iniparib, has distinct properties and appears promising in combination with chemotherapy (O'Shaughnessy 2011; [2.2]).

2.1 **Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition**



In normal cells, both base-excision repair (BER) and homologous recombination (HR) are available for the repair of damaged DNA. In cells that have lost BER function because of PARP1 inhibition but retain at least one functioning copy of BRCA1 and BRCA2, HR is intact and can repair DNA damage, including damage left unrepaired because of the loss of BER (A). In the cancer cells of mutation carriers, all BRCA1 or BRCA2 function is absent, and when PARP1 is inhibited, cancer cells are unable to repair DNA damage by HR or BER, and cell death results (B).

DR LOVE: Do you believe PARP inhibitors should be combined with chemotherapy, used alone, or are both options feasible?

PROF ASHWORTH: I believe it depends on the genetic background of the tumor. Tumors with a hard defect in homologous recombination DNA repair — such as those with BRCA mutations — will benefit from a single-agent PARP inhibitor. In contrast, tumors such as triple-negative breast cancer (TNBC), which might be considered to have a soft or minor defect in DNA repair, might benefit the most with additional DNA damage from chemotherapy.

Track 5

DR LOVE: Would you discuss the concept of BRCAness, particularly as related to triple-negative breast cancer, and whether predictive biomarkers exist for PARP inhibitors?

PROF ASHWORTH: BRCAness is a clinical situation in which a defect is present in the pathway of homologous recombination — not caused by BRCA mutations — and the tumors phenotypically resemble those with BRCA1 or BRCA2 mutations. An example is TNBC, which appears similar to tumors

2.2

Gemcitabine/Carboplatin with or without Iniparib (BSI-201) in Metastatic Triple-Negative Breast Cancer

	Gemcitabine/ carboplatin (n = 62)	Gemcitabine/ carboplatin + BSI-201 (n = 61)	Hazard ratio	*p*-value
ORR	32%	52%	—	0.02
PFS	3.6 months	5.9 months	0.59	0.01
OS	7.7 months	12.3 months	0.57	0.01

"The addition of iniparib to chemotherapy improved the clinical benefit and survival of patients with metastatic triple-negative breast cancer without significantly increased toxic effects. On the basis of these results, a Phase III trial adequately powered to evaluate overall survival and progression-free survival is being conducted."

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

O'Shaughnessy J et al. *N Engl J Med* 2011;364(3):205-14.

with BRCA1 mutations. We are still at a stage at which BRCAness is useful as a concept for discussing issues rather than being predictive for clinical benefit. However, one can imagine that in the future we may have assays for BRCAness that could involve measuring DNA repair processes in tumors and may eventually predict response to a PARP inhibitor.

One of the key proteins involved in DNA repair is RAD1, and it is switched on in response to DNA damage as a marker of homologous recombination. RAD1 binds to BRCA1 and BRCA2, which carry out the repair of double-strand breaks. Breast tumors not expressing RAD1 tend to resemble the BRCAness phenotype and appear similar to triple-negative tumors. If we could implement RAD1 in a prospective trial and validate it, then it might be used for patient selection.

DR LOVE: What are your thoughts on assays for PARP?

PROF ASHWORTH: One school of thought proposes that levels of PARP influence response to a PARP inhibitor. This is a traditional way of considering drug targets, and in my view this does not address the concept of synthetic lethality. However, PARP is activated by DNA damage, and it is possible that higher PARP levels are a surrogate of DNA repair defects. All the data are preliminary, and we would like to see, with proper studies conducted in a powered fashion, if PARP levels are related to response to treatment. ■

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Iglehart JD et al. **Synthetic lethality — A new direction in cancer drug development.** *N Engl J Med* 2009;361(2):123-34.

O'Shaughnessy J et al. **Iniparib plus chemotherapy in metastatic triple-negative breast cancer.** *N Engl J Med* 2011;364(3):205-14.

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.

INTERVIEW

Michael Untch, MD, PhD

Prof Untch is Head of the Breast Cancer Center at HELIOS Klinikum Berlin-Buch in Berlin, Germany.

Tracks 1-10

Track 1 GEPARQUINTO GBG 44 study: Lapatinib versus trastuzumab with neoadjuvant anthracycline/taxane-based chemotherapy in HER2-positive early BC

Track 2 Pathologic complete response rates with chemotherapy/trastuzumab versus chemotherapy/lapatinib in the neoadjuvant setting

Track 3 Perspective on the efficacy and tolerability of trastuzumab versus lapatinib in HER2-positive early BC

Track 4 Potential clinical implications of the NeoALTTO trial for adjuvant therapy in HER2-positive BC

Track 5 NeoSphere: A randomized Phase II study of neoadjuvant pertuzumab and trastuzumab

Track 6 GEPARQUINTO GBG 44 study: Neoadjuvant chemotherapy with or without bevacizumab for HER2-negative early BC

Track 7 Translational investigations to identify predictive biomarkers for biological agents in BC

Track 8 Patient selection for bevacizumab and chemotherapy in metastatic BC

Track 9 Evaluation of PARP expression as a predictor of response to chemotherapy or PARP inhibitors in BC

Track 10 Neoadjuvant PARP inhibitor trials in BC

Select Excerpts from the Interview

Tracks 1-2, 6

DR LOVE: Your German Breast Group (GBG) GEPARQUINTO GBG 44 study has an ambitious design that stratifies patients to neoadjuvant chemotherapy with or without differing biologic agents based on HER2 status. Would you discuss the results you reported at SABCS 2010 for patients with HER2-positive disease?

PROF UNTCH: The HER2-positive component of the GEPARQUINTO study evaluated 620 patients with HER2-positive early breast cancer. Patients were randomly assigned to 24 weeks of either trastuzumab or lapatinib with neoadjuvant chemotherapy with epirubicin/cyclophosphamide followed by four cycles of docetaxel.

This was the first clinical trial to compare chemotherapy/trastuzumab to chemotherapy/lapatinib. According to NSABP criteria, the pathologic complete response (pCR) rate was 50 percent with chemotherapy/trastuzumab and 35 percent with chemotherapy/lapatinib, which was unexpectedly lower than what was hypothesized at the beginning of this study (Untch 2010; [3.1]).

In the intent-to-treat analysis, 23 percent of patients on the chemotherapy/lapatinib arm had treatment discontinued, mainly because of Grade III or higher diarrhea, compared to a 13 percent rate of discontinuation in patients who received chemotherapy/trastuzumab.

This was the first time that lapatinib has been administered with anthracyclines and docetaxel, and we had to learn how to cope with the side effects of this combination. We learned that it was necessary to reduce the dose of lapatinib from 1,250 mg per day to 1,000 mg per day to avoid diarrhea, and we also learned to add G-CSF to avoid febrile neutropenia from lapatinib and docetaxel. These are important lessons learned from this trial, and we now discuss with patients which side effects to expect and how to deal with them.

The total cardiac failure rate on study with epirubicin/cyclophosphamide/trastuzumab was less than 0.5 percent. This experience is in line with previous experiences in Europe.

DR LOVE: What about the results reported by your colleague Dr von Minckwitz for patients with HER2-negative disease?

PROF UNTCH: We expected to see a signal with the addition of bevacizumab to neoadjuvant chemotherapy in the HER2-negative population, but the addition of bevacizumab to chemotherapy did not significantly increase the pCR rate overall (von Minckwitz 2010). The only subgroup of patients who seemed to benefit from the combination of chemotherapy and bevacizumab were the patients with triple-negative disease. We eagerly await further data

3.1

GEPARQUINTO GBG 44 Trial: Efficacy of Trastuzumab versus Lapatinib in Combination with Neoadjuvant Anthracycline/Taxane-Based Chemotherapy in HER2-Positive Early Breast Cancer

	T + EC-doc	L + EC-doc	*p*-value
pCR[1]	50.4%	35.2%	<0.05
pCR[2]	45.0%	29.9%	<0.05
pCR[3]	31.3%	21.7%	<0.05
Breast conservation rate	65.6%	56.0%	—

[1] No invasive residual cancer in breast only; [2] No invasive residual cancer in breast and nodes; [3] No invasive or noninvasive residual cancer in breast and nodes based on central pathology report review

T = trastuzumab; E = epirubicin; C = cyclophosphamide; doc = docetaxel; L = lapatinib; pCR = pathologic complete response

Untch M et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-1**.

on the use of chemotherapy/bevacizumab from the ongoing NSABP-B-40 and BEATRICE trials in early breast cancer.

Track 4

DR LOVE: What is your take on the neoadjuvant Phase III NeoALTTO trial, which evaluated lapatinib, trastuzumab and the combination with paclitaxel in patients with HER2-positive primary breast cancer?

PROF UNTCH: The concept of dual receptor targeting with lapatinib and trastuzumab is to attack the tumor cell from the outside with trastuzumab and from the inside with lapatinib. This principle was shown in the NeoALTTO trial, in which the authors reported an extremely nice synergistic effect (Baselga 2010; [3.2]). All of us wonder if this will also be the case with the more than 8,000-patient ALTTO study in the adjuvant setting. I would await additional results with dual receptor combination inhibitors before using that approach outside of a protocol in the adjuvant or neoadjuvant setting. ■

3.2

NeoALTTO: Pathologic Complete Response (pCR) Rates in a Phase III Neoadjuvant Trial of Lapatinib (L), Trastuzumab (T) and the Combination with Paclitaxel (P) in HER2-Positive Primary Breast Cancer

Response	**P + L** (n = 154)	**P + T** (n = 149)	**P + L + T** (n = 152)
pCR[1]	24.7%	29.5%	51.3%
	p-value: 0.34 (L vs T); 0.0001 (L + T vs T)		
	P + L (n = 150)	**P + T** (n = 145)	**P + L + T** (n = 145)
Total pCR[2]	20.0%	27.6%	46.9%
	p-value: 0.13 (L vs T); 0.001 (L + T vs T)		

[1] No invasive cancer in the breast; [2] No invasive cancer in the breast and lymph nodes (excludes 15 patients with nonevaluable nodal status)

Baselga J et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

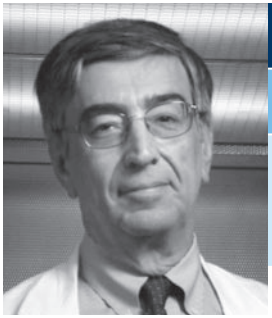
SELECT PUBLICATIONS

Baselga J et al. **First results of the NeoALTTO trial (BIG 01-06/EGF 106903): A Phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Chang HR. **Trastuzumab-based neoadjuvant therapy in patients with HER2-positive breast cancer.** *Cancer* 2010;116(12):2856-67.

Untch M et al. **Lapatinib vs trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S3-1**.

Von Minckwitz G et al. **Neoadjuvant chemotherapy with or without bevacizumab: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-6**.



INTERVIEW

Luca Gianni, MD

Dr Gianni is Director of Medical Oncology 1 in the Department of Medical Oncology at the Istituto Nazionale Tumori di Milano in Milan, Italy.

Tracks 1-6

Track 1	Mechanisms of action of pertuzumab and trastuzumab
Track 2	NeoSphere: A randomized Phase II trial investigating anti-HER2 agents in the neoadjuvant setting
Track 3	Planned clinical trial evaluating adjuvant trastuzumab/pertuzumab for HER2-positive early BC
Track 4	Neoadjuvant therapy for HER2-positive BC
Track 5	Trastuzumab in HER2-normal early BC
Track 6	Approach to patients with metastatic BC after adjuvant chemotherapy/trastuzumab

Select Excerpts from the Interview

Track 1

DR LOVE: What is known about the mechanism of action of pertuzumab?

DR GIANNI: Pertuzumab is a monoclonal antibody that targets the external domain of the HER2 receptor at a different location than trastuzumab (4.1). Because no steric hindrance occurs, the two monoclonal antibodies — pertuzumab and trastuzumab — can be used together. According to animal models, laboratory models and patient models, the combined use of trastuzumab and pertuzumab yields at least additive if not synergistic effects (Baselga 2010; Gianni 2010). In women with breast cancer, a recent trial in metastatic disease showed that the introduction of pertuzumab soon after the failure of trastuzumab was associated with an unexpectedly high response rate (Baselga 2010; [4.2]).

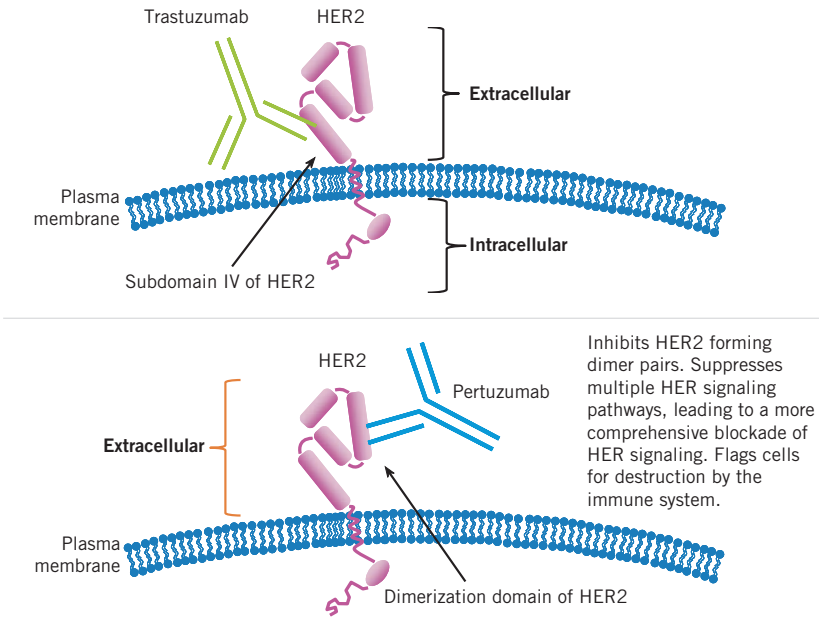
Track 2

DR LOVE: Would you discuss the NeoSphere trial findings that you presented in San Antonio?

DR GIANNI: The design of the trial was simple. We decided to evaluate the use of neoadjuvant drugs for HER2-positive breast cancer and to rank the efficacy of the treatments we tested. Because the laboratory and clinical data associ-

4.1

Targets of Trastuzumab and Pertuzumab on the Human Epidermal Growth Factor Receptor



Park Y et al. *World J Clin Oncol* 2011;2(2):125-34. With permission, © 2011 Baishideng Publishing Group.

ated with pertuzumab/trastuzumab were favorable, we also designed an arm on which women received only the two monoclonal antibodies for four cycles. We used conventional treatment, consisting of trastuzumab with docetaxel, as a comparator, and we also studied a triple combination of pertuzumab/trastuzumab/docetaxel. We found that the triple combination of docetaxel/trastuzumab/pertuzumab was associated with a high rate — 45.8 percent — of pCR in the breast, which was significantly higher than that of the conventional treatment with docetaxel and trastuzumab — 29 percent (4.3).

DR LOVE: Does anyone have plans to evaluate the combination of trastuzumab/pertuzumab in the adjuvant setting?

DR GIANNI: A trial has already been designed by the Breast International Group as a joint effort and is planned to launch by the end of 2011.

DR LOVE: Is there interest in studying the antibody combination in women who are not candidates for chemotherapy?

DR GIANNI: That is an important question. In the NeoSphere study, the two monoclonal antibodies were administered for only four cycles because the trial was designed to rank therapies, not to fully explore therapeutic potential. Because the NeoSphere study demonstrated that you can eradicate disease in

a subset of women with HER2-positive breast cancer without the addition of chemotherapy, the challenge is to further explore and identify a priori which women will benefit from this combination because the tolerability of this monoclonal regimen is so high. ■

4.2

Efficacy of Pertuzumab Combined with Trastuzumab During a Phase II Study for Women with Metastatic Cancer Whose Disease Progressed on Prior Treatment* with Trastuzumab-Containing Regimens

Best response	N = 66 (80% CI)
Complete response	7.6% (3.7-13.6)
Partial response	16.7% (10.9-24.1)
Stable disease ≥6 months	25.8% (18.8-33.9)
Progressive disease	50% (41.5-58.5)

* Patients received prior trastuzumab-based therapy for a mean of 16.2 months.

Baselga J et al. *J Clin Oncol* 2010;28(7):1138-44.

4.3

Efficacy of Neoadjuvant Trastuzumab and Pertuzumab by Breast and Lymph Node Status During the NeoSphere Study

	TH (n = 107)	THP* (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node-negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node-positive at surgery	7.5%	6.5%	5.6%	6.3%

T = docetaxel; H = trastuzumab; P = pertuzumab; pCR = pathologic complete response

* *p*-value was significant for THP versus all other arms for each outcome shown.

Gianni L et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

SELECT PUBLICATIONS

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

Gianni L et al. **Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized Phase II study ('NeoSphere').** San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

Gianni L et al. **Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer.** *J Clin Oncol* 2010;28(7):1131-7.

Scheuer W et al. **Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models.** *Cancer Res* 2009;69(24):9330-6.

INTERVIEW

Nicholas J Robert, MD

Dr Robert is Associate Chair of US Oncology Research Network's Breast Cancer Committee and Chairman of the Cancer Committee of Inova Fairfax Hospital's Cancer Center in Fairfax, Virginia.

Tracks 1-11

Track 1	**Case discussion:** A 73-year-old woman with TNBC experiences relapse five years after initial adjuvant dose-dense chemotherapy and enrolls on a clinical trial of iniparib (BSI-201) with chemotherapy
Track 2	Use of bevacizumab in the management of metastatic BC
Track 3	Clinical trial strategies for investigating PARP inhibitors in early BC
Track 4	Perspective on the choice of HER2-directed therapy in the adjuvant setting for HER2-positive early BC
Track 5	Biology and biomarker-driven personalized therapy for BC
Track 6	**Case discussion:** A 55-year-old woman with ER-positive, HER2-negative metastatic BC receives multiple hormonal therapies followed by enrollment on the RIBBON 1 trial of capecitabine/bevacizumab
Track 7	Antitumor efficacy of fulvestrant and relation to the dose used
Track 8	Use of the Onco*type* DX assay in patients with ER-positive, node-negative or node-positive BC in the adjuvant and neoadjuvant settings
Track 9	Treatment for patients with HER2-positive recurrent BC and prior exposure to trastuzumab
Track 10	Eribulin as a novel antitubular agent with efficacy in BC
Track 11	Challenges with overall survival as the primary endpoint for first-line therapy in metastatic BC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you tell us about your patient with TNBC?

DR ROBERT: This is a 73-year-old woman who initially presented with T2N1+ TNBC approximately six years ago. She received dose-dense chemotherapy in the adjuvant setting and experienced relapse four years later with biopsy-proven pleural disease. At the time of disease recurrence she received iniparib with carboplatin/gemcitabine in a randomized Phase II trial (O'Shaughnessy 2011; [2.2, page 8]). Her tolerance to the regimen was excellent, and her disease was controlled for approximately 18 months on iniparib with carboplatin/gemcitabine.

DR LOVE: What treatment would you have recommended off protocol?

DR ROBERT: If she had not enrolled on the iniparib trial, then at the time an alternative for her as a patient with TNBC would have been bevacizumab with weekly paclitaxel. When we incorporate bevacizumab into treatment of metastatic breast cancer, we generally use it in the first line with weekly paclitaxel.

DR LOVE: What do we know about chemotherapy with bevacizumab in patients with TNBC as opposed to those with other subtypes?

DR ROBERT: Several bevacizumab trials have taken place in the first-line metastatic breast cancer setting: ECOG-E2100, AVADO and RIBBON 1. These trials combined different chemotherapy regimens with bevacizumab. When evaluating the TNBC subset, we see enhanced efficacy when bevacizumab is added to chemotherapy (O'Shaughnessy 2010; [5.1]).

5.1

Meta-Analysis of Patients with Triple-Negative Breast Cancer Randomly Assigned in First-Line Trials of Chemotherapy with or without Bevacizumab for Metastatic Breast Cancer

	Bevacizumab + chemotherapy (n = 363)	Chemotherapy alone (n = 258)	HR	*p*-value
ORR	42%	23%	NR	<0.0001
Median PFS	8.1 months	5.4 months	0.649	<0.0001
12-month survival rate	70.9%	64.8%	NR	0.1140
Median OS	18.9 months	17.5 months	0.959	0.6732

HR = hazard ratio; ORR = objective response rate; NR = not reported; PFS = progression-free survival; OS = overall survival

O'Shaughnessy J et al. San Antonio Breast Cancer Symposium 2010;**Abstract P6-12-03**.

Track 8

DR LOVE: Would you comment on the data combining clinicopathologic factors with the Onco*type* DX RS that were presented at San Antonio (Tang 2010)?

DR ROBERT: My takeaway from the presentation is that we are still left with the current RS and the modification of the RS did not translate to be useful in the clinic.

With that said, until we have the results of the TAILORx trial, in a patient with an intermediate RS, a number of other clinical factors — such as age, tumor size and tumor grade — come into play.

In the case of a lower-grade, smaller tumor in an older patient with an intermediate RS, we are more comfortable administering endocrine therapy alone.

My older patients — that is, those who are postmenopausal — usually decline the idea of pursuing even a short course of adjuvant chemotherapy if they hear of any doubt about additional benefit with the adjuvant chemotherapy approach in the clinical setting.

Track 10

DR LOVE: Would you discuss what we know about eribulin?

DR ROBERT: Eribulin is a unique analog of the marine sponge natural product halichondrin B and is a potent mitotic inhibitor. Our group was involved in the pivotal randomized Phase III EMBRACE trial, which randomly assigned patients to eribulin or physician's choice.

The results of the trial showed improved outcomes on the eribulin arm (Twelves 2010; [5.2]). On the basis of the results of this trial, the drug was approved by the FDA and now adds to the armamentarium against metastatic breast cancer. ■

5.2

EMBRACE Trial: Eribulin versus Treatment of Physician's Choice (TPC) for Patients with Previously Treated Locally Recurrent or Metastatic Breast Cancer

Endpoint (ITT population)	Eribulin	TPC	Hazard ratio	*p*-value
Median OS (n = 508, 254)	13.1 mo	10.6 mo	0.81	0.041
Median PFS* (n = 508, 254)	3.7 mo	2.2 mo	0.87	0.14
ORR* (CR + PR) (n = 468, 214)	12.2%	4.7%	—	0.002
CBR* (CR + PR + SD) (n = 468, 214)	22.6%	16.8%	—	—

* Independent review

ITT = intent to treat; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; CBR = clinical benefit rate; SD = stable disease ≥6 months

Twelves C et al. *Proc ASCO* 2010;**Abstract CRA1004**.

SELECT PUBLICATIONS

O'Shaughnessy J et al. **Iniparib plus chemotherapy in metastatic triple-negative breast cancer.** *N Engl J Med* 2011;364(3):205-14.

O'Shaughnessy J et al. **Meta-analysis of patients with triple-negative breast cancer (TNBC) from three randomized trials of first-line bevacizumab (BV) and chemotherapy treatment for metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2010;**Abstract P6-12-03**.

Tang G et al. **Comparing the prediction of chemotherapy benefit in patients with node-negative, ER-positive breast cancer using the recurrence score and a new measure that integrates clinical and pathologic factors with the recurrence score.** San Antonio Breast Cancer Symposium 2010;**Abstract S4-9**.

Twelves C et al. **A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane.** *Proc ASCO* 2010;**Abstract CRA1004**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A higher proportion of women age 40 or younger have a high RS when compared to women age 41 to 69.**
   a. True
   b. False
2. **Which of the following has been shown to be a predictor of chemotherapy benefit in ER-positive, node-negative breast cancer?**
   a. RSPC
   b. RS
   c. Both of the above
   d. None of the above
3. **Which of the following disease types are included in the randomized Phase III SWOG-S1007 study of the use of RS?**
   a. ER-positive, node-negative
   b. ER-positive, node-positive
   c. ER-negative, node-negative
   d. ER-negative, node-positive
4. **Which of the following outcomes were improved in the randomized Phase II study of the addition of iniparib to carboplatin/gemcitabine in previously treated metastatic TNBC?**
   a. Overall response rate
   b. Progression-free survival
   c. Overall survival
   d. All of the above
5. **PARP inhibitors cause cell death in tumors with BRCA mutation by _____.**
   a. Direct cytotoxicity
   b. Inhibiting angiogenesis
   c. Synthetic lethality
6. **Analysis of patients with HER2-positive early breast cancer receiving trastuzumab versus lapatinib in combination with neoadjuvant anthracycline/taxane-based chemotherapy in the GEPARQUINTO GBG 44 study reported a higher pCR rate according to NSABP criteria with chemotherapy/trastuzumab than with chemotherapy/lapatinib.**
   a. True
   b. False
7. **Analysis of patients with HER2-negative early breast cancer receiving neoadjuvant anthracycline/taxane-based chemotherapy with or without bevacizumab on the GEPARQUINTO GBG 44 study reported a statistically significant benefit in pCR rate with chemotherapy/bevacizumab versus chemotherapy alone.**
   a. True
   b. False
8. **The neoadjuvant Phase III NeoALTTO trial, which evaluated lapatinib, trastuzumab and the combination with paclitaxel for patients with HER2-positive primary breast cancer, reported the highest pCR rate on the paclitaxel/lapatinib arm.**
   a. True
   b. False
9. **The NeoSphere trial found that the combination of pertuzumab, trastuzumab and docetaxel was associated with an in-breast pCR rate of approximately 20 percent.**
   a. True
   b. False
10. **A meta-analysis of patients with TNBC, randomly assigned in first-line trials of chemotherapy with or without bevacizumab for metastatic breast cancer, has shown that the addition of bevacizumab results in improvement in _____.**
    a. Overall response rate
    b. Progression-free survival
    c. Overall survival
    d. Both a and b
11. **The Phase III EMBRACE trial of eribulin versus treatment of physician's choice for previously treated breast cancer has shown that eribulin results in improvement in _____.**
    a. Objective response rate
    b. Progression-free survival
    c. Overall survival
    d. All of the above
    e. a and b only

Post-test answer key: 1a, 2b, 3b, 4d, 5c, 6a, 7b, 8b, 9b, 10d, 11d

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 1, 2011

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
Results of major neoadjuvant trials of anti-HER2-based therapy (GEPARQUINTO, NeoSphere, NeoALTTO)	4 3 2 1	4 3 2 1
Study evaluating the value of combining clinicopathologic information with the Onco*type* DX RS for the prediction of benefit from adjuvant chemotherapy in patients with ER-positive breast cancer	4 3 2 1	4 3 2 1
Clinical investigators' perspectives on the role of bevacizumab-based therapy in HER2-negative metastatic breast cancer	4 3 2 1	4 3 2 1
Putative mechanism of action of PARP inhibitors in BRCA1/2-mutant and/or triple-negative breast cancer and the concepts of oncogene addiction and synthetic lethality	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain:.....

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

☐ This activity validated my current practice; no changes will be made
☐ 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 one 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:

- Determine the utility of genomic assays for counseling patients with ER-positive early breast cancer about their risk of recurrence and the potential benefits of adjuvant chemotherapy..... 4 3 2 1 N/M N/A
- Develop evidence-based treatment approaches for patients with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings..... 4 3 2 1 N/M N/A
- Evaluate the unique mechanisms of action and emerging clinical data for novel anti-HER2 agents under investigation in breast cancer..... 4 3 2 1 N/M N/A
- Appraise the risks and benefits of bevacizumab-based therapy for patients with HER2-negative metastatic breast cancer..... 4 3 2 1 N/M N/A
- Summarize the presumed mechanism of action of PARP inhibitors in breast cancer, particularly in patients with BRCA1/2 mutations and/or triple-negative disease..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials..... 4 3 2 1 N/M N/A

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

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

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 TWO — 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
Sandra M Swain, MD	4 3 2 1	4 3 2 1
Professor Alan Ashworth, FRS	4 3 2 1	4 3 2 1
Michael Untch, MD, PhD	4 3 2 1	4 3 2 1
Luca Gianni, MD	4 3 2 1	4 3 2 1
Nicholas J Robert, 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 .....

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

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Breast Cancer® UPDATE

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UPDATE

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