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Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Neil L Spector, MD
Joyce O'Shaughnessy, MD
Chris Twelves, BMedSci, MBChB, MD
Fabrice Andre, MD, PhD

EDITOR

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CME Certified

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 and prognostic 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/oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Determine the utility of genomic assays in 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 HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Evaluate the unique mechanisms of action and the emerging clinical data with novel anti-HER2 agents under investigation in breast cancer.
- Formulate individualized approaches for first- and later-line therapy for patients with HER2-negative metastatic breast cancer.
- Summarize the presumed mechanism of action and clinical activity of PARP inhibitors in metastatic triple-negative breast cancer.

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INTERVIEW

Neil L Spector, MD

Dr Spector is Co-Director of the Experimental Therapeutics Program at Duke Cancer Institute in Durham, North Carolina.

Tracks 1-17

Select Excerpts from the Interview

Track 5

DR LOVE: What are your thoughts on some of the new agents being investigated for HER2-positive breast cancer?

DR SPECTOR: I find the T-DM1 story interesting. This agent uses the "magic bullet" approach by essentially capitalizing on the specificity and ability of an

antibody like trastuzumab to selectively seek out only those cells that overexpress HER2 on the tumor cell surface. A mechanism internalizes the antibody and protein into the cell. That internalization then leads to the release of maytansine, which is a poison that blocks protein synthesis.

Having only a few molecules of maytansine in a cell is highly toxic. T-DM1 is killing breast cancer cells that overexpress HER2, not necessarily through an immune-mediated response but by delivering a poison directly into the tumor cell. If we can deliver poison specifically to tumor cells and not normal tissue, then that's the "Holy Grail" of therapeutics (Hurwitz 2011; [1.1]).

1.1

Randomized Phase II Study of T-DM1 versus Trastuzumab and Docetaxel as First-Line Therapy for HER2-Positive Metastatic Breast Cancer

	T-DM1 (n = 67)	Trastuzumab/docetaxel (n = 70)	Hazard ratio	*p*-value
Median progression-free survival	14.2 mo	9.2 mo	0.594	0.0353

Conclusion: This is the first study to evaluate an antibody-drug conjugate for HER2-positive metastatic breast cancer compared to standard therapy. These results validate the hypothesis that the unique targeted delivery of chemotherapy through T-DM1 may lead to an improved therapeutic index.

Hurwitz S et al. European Multidisciplinary Cancer Congress 2011;**Abstract 5001**.

Track 6

DR LOVE: What are your thoughts about the NSABP trial evaluating adjuvant trastuzumab in HER2-low breast cancer (1.2), which is based on data from Soon Paik (Paik 2008)?

DR SPECTOR: I believe it's an intriguing observation that a subpopulation of women whose tumors do not overexpress HER2 still respond to trastuzumab. This points to the fact that patients may have HER2 expressed on their tumor cells that may not meet the definition of overexpression but may still be functionally relevant to those cells.

Is it because the HER2 that is not overexpressed in tumors that still may respond to trastuzumab is heavily phosphorylated? Perhaps this indicates that although the gene is not amplified, it's still being activated through some mechanism that we don't fully understand. Maybe it's being activated through its association with HER3 or EGFR.

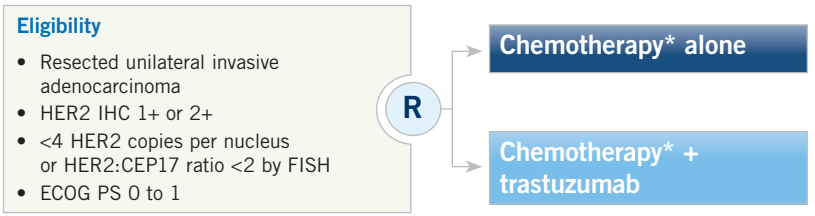
Tracks 10-11

DR LOVE: Would you discuss the issues of acquired resistance to trastuzumab and why patients who clinically become resistant to trastuzumab often still have HER2 overexpression?

1.2

NSABP-B-47: A Phase III Trial of Adjuvant Chemotherapy with or without Trastuzumab for Patients with Node-Positive or High-Risk Node-Negative, HER2-Normal Invasive Breast Cancer

Protocol IDs: CDR0000692574; NCT01275677 **Target Accrual:** 3,260 (Open)



* Investigator preference: Docetaxel/cyclophosphamide OR doxorubicin/cyclophosphamide → paclitaxel

www.clinicaltrials.gov, November 2011.

DR SPECTOR: Changes may be occurring in the immune response because trastuzumab relies heavily on an immune effect, and changes may affect the ability of the immune system to respond to those cells that are bound by trastuzumab. In addition, other receptors such as insulin-like growth factor 1 receptor (IGF1R) on the surface of HER2-positive breast cancer cells may be involved in mediating the development of resistance. Several therapeutic strategies involving IGF1R are now in clinical development.

Some evidence exists that IGF1R may take over some of the survival regulation in HER2-positive breast cancer cells that have been treated with trastuzumab. My analogy is when you shut down one light switch, another switch keeps the room lit. So we are interested in an approach that combines trastuzumab with inhibitors of IGF1R.

Evidence suggests that PI3 kinase mutations, which are prevalent in breast cancer, mediate resistance to trastuzumab and potentially to lapatinib as well (Wang 2011). That is a downstream event, not something on the cell surface and not another light switch that you haven't shut down. It's essentially a screwup in the wiring within the wall, which makes the cell independent of the receptor. It doesn't matter whether you turn the switch off or on — you need to go in and cut the wiring. Therefore, combining trastuzumab with small molecule inhibitors of PI3 kinase and mTOR is of interest.

Another hypothesis surrounding response to trastuzumab centers on truncation of the HER2 receptor. A truncated HER2 receptor is missing the extracellular domain — the part of the receptor that "flaps in the breeze" in the bloodstream. This is part of the receptor that is the target for trastuzumab and likely also for pertuzumab and T-DM1. You can imagine that in a patient with breast cancer whose tumor has a lot of truncated HER2 the antibody is no longer going to be effective. But that truncated receptor is still signaling and promoting the growth, survival and metastatic progression of that tumor.

Women with HER2-positive breast cancer with evidence of truncated HER2 may have a completely different clinical outcome than women who have no evidence of truncated HER2 (Scaltriti 2007). It has been suggested that small molecule tyrosine kinase inhibitors (TKIs), which get into the cell and affect the portion of the truncated HER2 receptor that is still active, may be more beneficial for women who have evidence of truncated HER2.

I believe that this will be a discriminating factor when recommending that women receive an antibody-based HER2-targeted therapy or potentially a TKI HER2-targeted therapy. That approach is now being tested in clinical trials. We've been limited to date in that we do not have good assays for truncated HER2 receptors. I hope that in the next 5 years we'll have that capability.

Tracks 12-13

DR LOVE: What is your perspective on the use of anti-HER2 therapies in other solid tumors?

DR SPECTOR: I believe some people have a tendency to say, "We did FISH and IHC and this tumor overexpresses HER2, and therefore we need to jump right in with HER2-targeted therapies without understanding the full milieu of what that tumor is." HER2-positive inflammatory breast cancer (IBC) is different from HER2-positive noninflammatory breast cancer, so even within breast cancer, factors make one type of HER2-positive breast cancer much more sensitive to HER2-targeted therapies than another.

We also need to understand some of these other tumor types. I'd hate to see clinical trials evaluating trastuzumab, lapatinib and other HER2-targeted therapies come up with less than impressive data and lead to a decision that this approach will never have an impact on nonbreast and nongastric HER2-overexpressing cancer. It would be wise to try to understand the biology and use these combinations more judiciously.

I would propose that we should be moving more toward a molecular phenotype denominator. I don't care whether it's proteomic, genomic, metabolomic or combinations of all of the above. I find it unconscionable that we'll spend 25 years going through each tumor type individually when, in fact, maybe what we need is to spend more time understanding the biology, then perform clinical trials based on a signature and have an approval based on a molecular type as opposed to a tumor type. ■

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Paik S et al. **HER2 status and benefit from adjuvant trastuzumab in breast cancer.** *N Engl J Med* 2008;358(13):1409-11.

Scaltriti M et al. **Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer.** *J Natl Cancer Inst* 2007;99(8):628-38.

Wang L et al. **PI3K pathway activation results in low efficacy of both trastuzumab and lapatinib.** *BMC Cancer* 2011;11:248.

INTERVIEW

Joyce O'Shaughnessy, MD

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

Tracks 1-16

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you discuss the biologic rationale for your study of iniparib for patients with triple-negative breast cancer (TNBC)?

DR O'SHAUGHNESSY: This trial was based on the concept of synthetic lethality, which means that a tumor cell in which BRCA1 or BRCA2 doesn't work properly is reliant on PARP for its DNA repair. So if you hit the cell with DNA-damaging chemotherapy and then also inhibit PARP, the cell dies because it has no way to repair its DNA.

We performed a Phase II trial of the PARP inhibitor iniparib in patients with TNBC (O'Shaughnessy 2011b) because data exist showing that some cases of TNBC are like BRCA1-related tumors, which have a substantial defect in their ability to repair double-strand breaks.

We didn't have a way to select for patients with problems with homologous recombination, the double-strand DNA repair mechanism, so we included "all comers" with TNBC in the randomized Phase II trial.

We chose gemcitabine/carboplatin (GC) because they are both DNA-damaging agents leading to single-strand breaks, which are converted to double-strand breaks in rapidly proliferative cancer such as TNBC. Among 123 patients with TNBC we observed a large improvement in overall and progression-free survival, response rates and clinical benefit rates even though 51% of patients who received GC alone crossed over to GC and iniparib at the time of disease progression (O'Shaughnessy 2011b).

For the Phase III trial we entered the same patient population. We enrolled 519 patients with rapid recruitment, with many patients who'd received adjuvant doxorubicin with cyclophosphamide followed by a taxane entering our trial immediately after disease recurrence. We had a higher rate of cross-over on the Phase III trial — 96% of patients on the GC arm who experienced disease progression crossed over to GC and iniparib.

Much to our disappointment, we did not see a statistically significant improvement in the coprimary endpoints of progression-free and overall survival (O'Shaughnessy 2011a; [2.1]). If we'd had one or the other as a primary endpoint, the study would have been positive.

We did report a signal in the second- and third-line patient population. The data looked good (2.1), but perhaps it's not large enough in a mixed population of patients to make it significant. It is possible that what's buried in that signal is a subpopulation of patients who benefit from this combination. Everyone agrees that's what we must find out.

An enormous amount of work is now ongoing to evaluate the patient populations between the Phase II and Phase III trials. We saw tremendous variability among patient subtypes in the Phase III trial.

TNBC is heterogeneous. Thus the hope is that we will be able to identify a subtype of TNBC in which GC and iniparib provide a benefit. By the end of the year, we plan to have an answer to that question. An important finding that's come to light is that although iniparib inhibits PARP as a protein, the physiologically achievable concentrations of iniparib we administer in humans are not inhibiting PARP.

2.1

Phase III Trial of Gemcitabine/Carboplatin (GC) with or without Iniparib (I) for Metastatic Triple-Negative Breast Cancer

	GC (n = 258)	GCI (n = 261)	Hazard ratio	*p*-value
Intent-to-treat (ITT) population				
Median OS	11.1 mo	11.8 mo	0.88	0.280
Median PFS	4.1 mo	5.1 mo	0.79	0.027
Exploratory analysis: Second-/third-line ITT population				
	GC (n = 109)	GCI (n = 113)	Hazard ratio	*p*-value
Median OS	91 mo	108 mo	0.65	0.012
Median PFS	29 mo	43 mo	0.67	0.011

OS = overall survival; PFS = progression-free survival

O'Shaughnessy J et al. *Proc ASCO* 2011a;**Abstract 1007**.

An interesting report from Dr Ji and colleagues analyzed olaparib, veliparib and iniparib in a TNBC cell line. They reported evidence of DNA-damaged double-strand breaks with all 3 agents. However, when they performed gene expression profiling on the cell lines to ascertain what was being inhibited, they found that olaparib and veliparib inhibited PARP1 and PARP2 but iniparib did not.

What they found was that iniparib was interfering with maintenance of telomeres, which are the ends of the chromosomes that need to be maintained by a whole host of enzymes for the chromosomes to be able to continue to divide (Ji 2011).

Telomeres are extremely important to these rapidly growing cells, and when you inhibit the telomere pathway, you get a crushing amount of DNA damage and the cell has a necrotic-like death.

Tracks 10-11

DR LOVE: What are your thoughts on the use of eribulin for patients with metastatic breast cancer (mBC)?

DR O'SHAUGHNESSY: Eribulin is an interesting new agent that was approved by the FDA late last year. We have to exercise caution in the setting of elevated liver function, but if you refer to the package label insert for eribulin, you'll see that for up to a Child-Pugh A category you're allowed to administer eribulin at a lower dose (2.2).

With the taxanes, ixabepilone and vinorelbine, we don't go near a patient with elevated bilirubin. I find the eribulin package insert and safety experience with lower doses helpful.

I have recently administered eribulin to a patient in this setting. Her disease had progressed through a number of treatments and she had come in with elevated bilirubin, significant ascites and lower-extremity edema. I administered reduced-dose eribulin, and her liver function tests improved. She diuresed about 45 pounds, had no ascites and the bilirubin normalized.

I'm also extremely impressed with the non-cross resistance of eribulin with the other agents we use in patients with metastatic disease. I'm trying to understand where else I can administer eribulin now.

For my own practice experience, I'd like to know more about the more classical triple-negative type that's not a BRCA1 germline mutation. In the EMBRACE trial, if you evaluate the forest plot with regard to overall survival, the point estimate is clearly in favor of eribulin, and it's as favorable in the triple-negative population (Cortes 2011b). ■

2.2

Dose and Administration of Eribulin Mesylate for Patients with Metastatic Breast Cancer and Impaired Liver Function

Recommended dose — administered IV over 2 to 5 minutes on days 1 and 8 of a 21-day cycle

Patients with **normal** hepatic function	Patients with **mild** hepatic impairment (Child-Pugh A)	Patients with **moderate** hepatic impairment (Child-Pugh B)
1.4 mg/m^2	1.1 mg/m^2	0.7 mg/m^2

Eribulin mesylate [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2010. Available at: **http://us.eisai.com/pdf_files/Halaven_PI.pdf**.

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Cortes J, Vidal M. **Beyond taxanes: The next generation of microtubule-targeting agents.** *Breast Cancer Res Treat* 2011a;[Epub ahead of print].

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* 2011b;377(9769):914-23.

Eribulin mesylate [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2010. Available at: **http://us.eisai.com/pdf_files/Halaven_PI.pdf**.

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Ji J et al. **Pharmacodynamic and pathway analysis of three presumed inhibitors of poly (ADP-ribose) polymerase: ABT-888, AZD2281, and BSI201.** *Proc AACR* 2011;**Abstract 4527**.

Lin NU, Burstein HJ. **EMBRACE, eribulin, and new realities of advanced breast cancer.** *Lancet* 2011;377(9769):878-80.

O'Shaughnessy J et al. **A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ASCO* 2011a;**Abstract 1007**.

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

INTERVIEW

Chris Twelves, BMedSci, MBChB, MD

Dr Twelves is Professor of Clinical Pharmacology and Oncology and Head of the Clinical Cancer Research Groups at the Leeds Institute of Molecular Medicine and St James's Institute of Oncology in Leeds, United Kingdom.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: You were heavily involved in the research development of capecitabine in both breast and colorectal cancer. How do you approach the dose and schedule of that agent today?

DR TWELVES: In a word, flexibly. I still use the 14-days-on, 7-days-off schedule, and for a fit, active patient I start with the full 2.5-g/m^2 dose, but I don't have a problem starting at the lower dose. Much debate has taken place about what that should be, and we published data a few years ago suggesting that more toxicity occurred with the full starting dose in the United States than elsewhere (Haller 2008).

Even if you start at the lower initial dose, many patients need modifications. I encourage using a low threshold for dose reducing, and I ask patients about

emerging toxicities. I prefer to dose reduce sooner rather than later, with the aim of maintaining treatment for as long as possible.

Tracks 6-10, 12

DR LOVE: You were also involved in the development of the antimicrotubule agent eribulin. Can you talk a bit about how that came about?

DR TWELVES: During the past 15 or 20 years, a focus has developed on marine organisms as a source of chemotherapy agents.

Eribulin, which was originally identified as an extract from a marine sponge, targets something that we consider a validated target — microtubules. We use vinca alkaloids and taxanes, so we know that targeting microtubules is a good approach, but eribulin was sufficiently novel to be of interest because it binds to microtubules in a different manner.

DR LOVE: Would you review the EMBRACE study?

DR TWELVES: EMBRACE was a large trial for patients with heavily pretreated disease (Cortes 2011; [3.1]). All patients had previously received an anthracycline, a taxane and up to 5 lines of prior chemotherapy. The patients on the treatment of physician's choice arm received a wide variety of therapies.

We first presented the overall survival data at ASCO 2010. At the time, no trial had been completed in which overall survival was achieved as the primary endpoint. The improvement in median survival was 2.5 months, and the increase in median survival represented a 23% improvement.

In the first analysis, only 55% of the events within the trial had occurred among the 750 patients on trial, so the data were relatively immature and the survival

3.1

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	0.137
ORR* (CR + PR) (n = 468, 214)	12%	5%	—	0.002
CBR* (CR + PR + SD) (n = 468, 214)	23%	17%	—	—

* 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

Cortes J et al. *Lancet* 2011;377(9769):914-23.

curves appeared to converge toward the lower portion. The *p*-value was 0.041, which some argued was barely significant. In the second analysis, however, the median improvement in survival increased from 2.5 to 2.7 months.

DR LOVE: How does the differential effect of age play into these results?

DR TWELVES: The benefits appear similar. When evaluating the age groups in terms of toxicity and efficacy, no obvious detriment or loss of efficacy is evident in older patients (Twelves 2011; [3.2]).

In terms of individual toxicities, the myelosuppression is real. If you take blood counts often enough, you see Grade III or IV neutropenia in up to half of the patients, but less than 5% of patients experience neutropenic sepsis. In our study, a little more than 8% of patients experienced Grade III or IV neuropathy (Twelves 2011; [3.3]).

We have a sister trial to the EMBRACE trial for patients with slightly less heavily pretreated disease (3.4). Those patients had not previously received capecitabine and were randomly assigned to the same experimental arm as in EMBRACE, which was compared to capecitabine. Hopefully we'll see the data in a year or so.

We're also studying eribulin and capecitabine in combination. We haven't presented data yet, but we haven't seen any unexpected toxicities. The combination is active, and we're looking to move into an expanded group of patients with mBC to obtain a better feel for clinical activity and toxicity.

DR LOVE: What about bringing eribulin into the adjuvant setting?

DR TWELVES: We don't have a head-to-head comparison of eribulin to another chemotherapy agent, but I believe we'll be more confident to move earlier in the disease once that has been conducted. Investigators are already piloting studies with other combinations, including combinations that ultimately might be used in the neoadjuvant or adjuvant settings. ■

3.2

Relationship between Age and Survival Outcomes with Eribulin in the Phase III EMBRACE Trial in Metastatic Breast Cancer

	ITT population			Response-evaluable population		
Age at recruitment	N	OS	PFS	N	ORR	CBR
<50	161	11.8 mo	3.5 mo	146	14.4	21.9
50-59	174	13.6 mo	3.7 mo	157	14.7	24.2
60-69	129	13.8 mo	3.8 mo	123	8.1	22.0
≥70	44	14.2 mo	4.2 mo	42	7.1	21.4

ITT = intent to treat; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; CBR = clinical benefit rate

Twelves C et al. *Proc ASCO* 2011;**Abstract 1060**.

3.3

EMBRACE Trial: Age-Based Assessment of Grade 3 and 4 Adverse Events with an Occurrence Rate of 5% or Higher

	Age <50 n = 160	Age 50-59 n = 171	Age 60-69 n = 128	Age ≥70 n = 44
Febrile neutropenia	5.0%	4.1%	3.9%	4.5%
Leukopenia	11.3%	15.2%	15.6%	13.6%
Neutropenia	36.9%	50.3%	46.9%	50.0%
Asthenia	2.5%	4.7%	6.3%	13.6%
Fatigue	3.1%	2.9%	3.9%	6.8%
Dyspnea	2.5%	2.3%	6.3%	9.1%

Twelves C et al. *Proc ASCO* 2011;**Abstract 1060**.

3.4

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

Protocol ID: NCT00337103

Target Accrual: 1,100 (Closed)

Eligibility

Locally advanced or metastatic breast cancer

≤3 prior chemotherapies, including an anthracycline and a taxane

No prior treatment with capecitabine

ECOG ≤ 2

R

- Eribulin 1.4 mg/m², d1, 8 q21d
- Capecitabine 2.5 g/m², d1-14 q21d

www.clinicaltrials.gov. Accessed November 2011.

SELECT PUBLICATIONS

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Twelves C et al. **The relationship between age and survival outcomes for eribulin in metastatic breast cancer.** *Proc ASCO* 2011;**Abstract 1060**.

INTERVIEW

Fabrice Andre, MD, PhD

Dr Andre is Associate Professor in the Department of Medical Oncology at the Institute Gustave Roussy in Villejuif, France.

Tracks 1-9

Select Excerpts from the Interview

Track 2

DR LOVE: What is your perspective on the utility of the Onco*type* DX assay in node-negative and node-positive breast cancer?

DR ANDRE: We have enough evidence to consider that Recurrence Score (RS) can identify a group of patients with ER-positive, node-negative disease who do not derive a large benefit from adjuvant chemotherapy. The RS has such a strong prognostic value in node-negative disease that you don't need to add chemotherapy for patients with a low RS — the rate of metastasis is below 10% at 10 years.

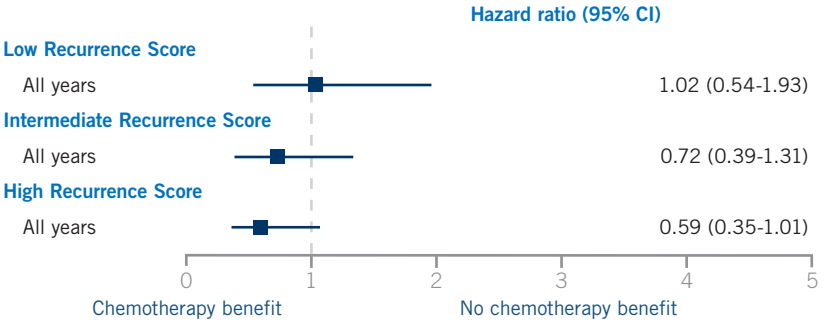
The picture is less clear in node-positive disease. A study by Kathy Albain reported that patients with a low RS do not derive a large benefit from anthracycline-based chemotherapy (Albain 2010; [4.1]). Still, node-positive

disease has its pitfalls, the first being that no one has yet shown the predictive value of RS for a taxane.

Second, the amount of evidence is minimal for RS in the node-positive setting. That said, I'm aware that the RxPONDER trial is now open to address the value of the RS in node-positive disease (4.2). This is important in distinguishing between the prediction of the value of adjuvant chemotherapy and the prognostic value of the RS.

4.1

Disease-Free Survival Hazard Ratios for Tamoxifen Alone versus CAF-T According to Recurrence Risk Group



Albain KS et al. *Lancet Oncol* 2010;11(1):55–65.

4.2

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

Protocol IDs: SWOG-S1007; RxPONDER

Target Accrual: 4,000

Eligibility
- Node-positive (1 to 3 nodes) breast cancer
- ER/PR-positive, HER2-negative
- Recurrence Score by Oncotype DX ≤25

R

- Endocrine therapy x 5 to 10 years
- Adjuvant chemotherapy based on patient and/or physician preference followed by endocrine therapy x 5 to 10 years

www.clinicaltrials.gov. Identifier NCT01272037, November 2011.

Tracks 8-9

DR LOVE: What are your thoughts on the NEOSPHERE study evaluating pertuzumab with trastuzumab and Neo-ALTTO trial data (trastuzumab and lapatinib) on dual anti-HER2 blockade?

DR ANDRE: The data show that with dual blockade in the neoadjuvant setting, an increase occurs in the pathologic complete response (pCR) rate (Baselga 2010; Gianni 2010; [4.3]). This means that targeting different parts of the same HER2 receptor could increase the efficacy of trastuzumab.

Many unknowns exist, such as the extent to which the improvement in pCR rates translates into improvement in progression-free survival, overall survival, et cetera. This should be answered by several ongoing adjuvant trials, including the ALTTO trial, which is evaluating trastuzumab versus trastuzumab/lapatinib versus lapatinib.

DR LOVE: Where do you see pertuzumab fitting into your treatment strategy for patients with early and advanced HER2-positive breast cancer?

DR ANDRE: Pertuzumab should be further developed in the setting of relapse after treatment with trastuzumab because, in the neoadjuvant setting, we have evidence that adding pertuzumab to trastuzumab improves pCR (4.3). ■

4.3

NEOSPHERE Study: Pathologic Complete Response (pCR) in the Breast and Lymph Node Status of Patients Receiving Neoadjuvant Trastuzumab and/or Pertuzumab

	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

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

SELECT PUBLICATIONS

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

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**.

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**.

Gonzalez-Angulo AM et al. **SWOG S1007: A phase III, randomized clinical trial of standard adjuvant endocrine therapy with or without chemotherapy in patients with one to three positive nodes, hormone receptor (HR)-positive, and HER2-negative breast cancer with recurrence score (RS) of 25 or less.** *Proc ASCO* 2011;**Abstract TPS104**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **T-DM1 is a novel agent that combines a maytansine derivative with _____.**
   a. Docetaxel
   b. Trastuzumab
   c. Bevacizumab
   d. None of the above

2. **PARP inhibitors with chemotherapy cause cell death in tumors with BRCA mutations through _____.**
   a. Direct cytotoxicity
   b. Inhibition of angiogenesis
   c. Synthetic lethality

3. **Updated data from ASCO 2011 from a Phase III trial of gemcitabine/carboplatin with or without iniparib in TNBC demonstrated a statistically significant improvement in both overall survival and progression-free survival.**
   a. True
   b. False

4. **A retrospective analysis of the SWOG-8814 study suggested that postmenopausal patients with ER-positive, node-positive disease and a(n) _____ Onco*type* DX RS did not experience significant benefits from the addition of adjuvant CAF chemotherapy to tamoxifen.**
   a. High
   b. Low
   c. Intermediate
   d. All of the above

5. **In a randomized Phase II study, which of the following first-line anti-HER2 treatments resulted in a superior progression-free survival for patients with HER2-positive metastatic breast cancer?**
   a. Trastuzumab/docetaxel
   b. T-DM1
   c. Neither — no significant difference was observed

6. **The NSABP-B-47 study is comparing the effects of chemotherapy with or without trastuzumab in patients with node-positive or high-risk node-negative, HER2-normal early breast cancer.**
   a. True
   b. False

7. **In the Phase III EMBRACE study, eribulin resulted in a significant improvement in overall survival compared to treatment of physician's choice for patients with previously treated mBC.**
   a. True
   b. False

8. **In an analysis of EMBRACE results by age, older patients clearly experienced less improvement in overall survival and significantly more adverse events compared to the overall population.**
   a. True
   b. False

9. **Which of the following is an eligibility criterion for the SWOG-S1007 (RxPONDER) Phase III study of adjuvant endocrine therapy with or without chemotherapy?**
   a. Node-positive (1 to 3 nodes only)
   b. ER-positive, HER2-negative
   c. Onco*type* DX RS ≤25
   d. All of the above

10. **The randomized Phase II neoadjuvant NEOSPHERE study demonstrated that the addition of pertuzumab to trastuzumab and chemotherapy resulted in an improvement in the pathologic complete response rate.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 3, 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
Mechanisms of action of trastuzumab, lapatinib and investigational agents in HER2-positive breast cancer	4 3 2 1	4 3 2 1
Determinants of response and acquired resistance to trastuzumab in HER2-positive breast cancer	4 3 2 1	4 3 2 1
Phase III study results of carboplatin/gemcitabine with iniparib in metastatic TNBC	4 3 2 1	4 3 2 1
Background and results of the Phase III EMBRACE study: Eribulin versus treatment of physician's choice in heavily pretreated mBC	4 3 2 1	4 3 2 1
Prediction of chemotherapy benefit with the Onco*type* DX RS in ER-positive early breast cancer	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 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:

- Determine the utility of genomic assays in 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 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 the emerging clinical data with novel anti-HER2 agents under investigation in breast cancer. ..... 4 3 2 1 N/M N/A
- Formulate individualized approaches for first- and later-line therapy for patients with HER2-negative metastatic breast cancer. ..... 4 3 2 1 N/M N/A
- Summarize the presumed mechanism of action and clinical activity of PARP inhibitors in metastatic triple-negative breast cancer. ..... 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
Neil L Spector, MD	4 3 2 1	4 3 2 1
Joyce O'Shaughnessy, MD	4 3 2 1	4 3 2 1
Chris Twelves, BMedSci, MBChB, MD	4 3 2 1	4 3 2 1
Fabrice Andre, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Other comments about the faculty and editor for this activity:

.....

Please recommend additional faculty for future activities:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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City, State, Zip: .....

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

Email: .....

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

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

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/BCU311/CME.

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Breast Cancer® UPDATE

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Breast Cancer®
UPDATE

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