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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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CME Certified

Breast Cancer Update for Surgeons
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Historically, surgery has been the primary mode of treatment for early breast cancer. The diagnostic, surgical and medical management of breast cancer, however, has escalated in complexity because of numerous advances in novel technologies and available adjunctive medical therapies. Hence, the multifaceted treatment of breast cancer now requires the input of an interdisciplinary group of expert care providers. This paradigm shift has created the challenge of ensuring that major clinical advances in local and systemic breast cancer therapy are effectively disseminated among all members of the cross-functional team. To bridge the gap between research and patient care, *Breast Cancer Update* for Surgeons utilizes one-on-one interviews with leading breast cancer investigators to translate the latest research developments into clinical practice. By providing access to cutting-edge data and expert perspectives, this CME program assists breast surgeons in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Utilize genomic assays to quantify recurrence risk and aid in individualized recommendations for systemic therapy for postmenopausal patients with ER-positive, node-negative or node-positive breast cancer.
- Evaluate issues related to the accuracy, reliability and interpretation of the ER and HER2 status of breast tumors in the context of local laboratory practices and national guidelines.
- Consider emerging data for sentinel lymph node evaluation and complete axillary dissection for documented micrometastases in surgical practice.
- Assess the clinical utility of preoperative magnetic resonance imaging for breast cancer detection and diagnosis.
- Identify patients with DCIS who may benefit from surgical resection without radiation therapy.
- Evaluate the risks and benefits of partial breast irradiation.
- Summarize the emerging data on select novel therapeutic agents or regimens in the treatment of early and metastatic breast cancer.
- Describe current approaches and ongoing clinical trials addressing the treatment of HER2-positive early breast cancer.
- Counsel appropriately selected patients about the option of participating in ongoing clinical trials.

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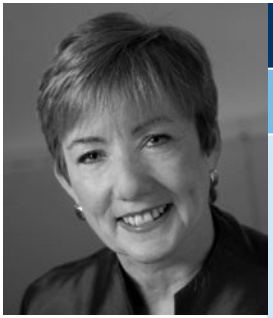

INTERVIEW

Monica Morrow, MD

Dr Morrow is Chief of the Breast Service in the Department of Surgery at Memorial Sloan-Kettering Cancer Center, Anne Burnett Windfohr Chair of Clinical Oncology and Professor of Surgery at Weill Medical College of Cornell University in New York, New York.

Tracks 1-14

Track 1 Reduced local recurrence rates with targeted therapy in early breast cancer (BC)

Track 2 Adequacy of margins for breast-conserving surgery

Track 3 Utility of the Onco*type* DX® Recurrence Score® (RS) for postmenopausal patients with ER-positive, node-negative or node-positive BC

Track 4 Surgical removal of primary BC in patients with de novo metastatic BC (mBC) in the era of targeted therapy

Track 5 Results of ECOG-E5194: Local therapy alone without radiation therapy for ductal carcinoma in situ (DCIS)

Track 6 Current role of partial breast irradiation (PBI) in DCIS and invasive BC

Track 7 Relationship between routine pretreatment MRI and mastectomy rate, margin status and local control

Track 8 Pending results of ACOSOG-Z0011: Axillary node dissection in women with clinical T1-2N0M0 BC who have a positive sentinel node

Track 9 **Case discussion:** A 46-year-old woman with small breasts and a 4-cm, ER-negative, HER2-positive, clinically node-negative BC desires breast conservation

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Track 14 **Case discussion:** A 60-year-old woman with a 2.5-cm, Grade II, strongly ER-positive, PR-positive, HER2-negative infiltrating ductal carcinoma (IDC) and two negative sentinel nodes with a low RS on the Onco*type* DX assay

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Where does the "new biology" of breast cancer fit into the surgical management of early breast cancer?

DR MORROW: We are entering an era in which we are considering not only disease burden in surgery but also the molecular biology of the tumor. It's increasingly apparent that not only survival but also local control are strongly influenced by molecular features of the tumor and the availability of targeted therapy. The interesting facet that was overshadowed by the dramatic disease-free survival advantage in the initial studies of adjuvant trastuzumab was the fact that the number of locoregional recurrences (LRR) was halved by the addition of trastuzumab to adjuvant chemotherapy (Romond 2005).

I believe that this is the same effect as that observed with tamoxifen and aromatase inhibitors, in which targeted therapy reduces local failure. We see that same hint in data from Onco*type* DX, although that assay was initially developed to predict the risk of distant recurrence. Terry Mamounas has published results evaluating the prediction of LRR on the basis of Onco*type* DX Recurrence Score and treatment (Mamounas 2010; [1.1]).

For patients with low-risk scores, the addition of tamoxifen substantially decreased the risk of local recurrence. For patients with high-risk scores who received only tamoxifen, LRR rates did not decrease much. Only with the addition of chemotherapy to tamoxifen were LRR rates substantially reduced for patients with high-risk scores (Mamounas 2010).

I believe that this is an important message for surgeons because it indicates that it's time to stop focusing strictly on margins and start thinking about the disease in a more biological way. An adequate margin might not be the same for all disease subtypes. Clearly, for women with ER/PR-positive disease receiving endocrine therapy, local control is good, and it's difficult for me to believe that any margin bigger than "tumor not touching ink" is important (Azu 2010).

For patients with triple-negative disease — for whom local recurrence rates are higher — it's tempting to speculate that a larger negative margin might be important, but the fact that after mastectomy this group of patients still has the highest local recurrence rate suggests that may not be true.

1.1

Association between Onco*type* DX Recurrence Score (RS) and Risk of Locoregional Recurrence for Patients with ER-Positive, Node-Negative Disease

	Ten-year locoregional recurrence rate		
Risk group	Placebo (n = 355)	Tamoxifen (n = 895)	Chemotherapy + tamoxifen (n = 424)
Low (RS < 18)	10.8%	4.3%	1.6%
Intermediate (RS = 18-30)	20.0%	7.2%	2.7%
High (RS ≥ 31)	18.4%	15.8%	7.8%

Mamounas EP et al. *J Clin Oncol* 2010;28(10):1677-83.

Track 3

DR LOVE: Would you discuss the utility of the Onco*type* DX assay for node-negative and node-positive breast cancer?

DR MORROW: The principle behind Onco*type* DX clearly makes sense for both node-negative and node-positive disease, namely that differences in prognosis exist and the assay predicts sensitivity to conventional chemotherapy.

I believe that the concern physicians have with using the assay for patients with node-positive disease is that the residual risk of relapse, even after endocrine therapy, is high enough for most of these patients that it's difficult to say, "We're not going to administer additional systemic treatment."

DR LOVE: Who should be ordering the Onco*type* DX assay — the surgeon or the medical oncologist?

DR MORROW: At Memorial Sloan-Kettering Cancer Center, we believe that the surgeon should order the test to incorporate it more rapidly. We order it for patients with HER2-negative, ER-positive, node-negative disease and tumors five millimeters or larger. The exception in this setting would be the patient who says, "I don't care how little the benefit is — I want chemotherapy." In that situation, we don't order the test.

I also find the assay helpful for patients who indicate that they are not interested in receiving chemotherapy, because with a low-risk score we can be reassured and with a high-risk score, women sometimes change their minds regarding systemic therapy when confronted with additional information about the biology of their cancer.

Track 4

DR LOVE: Would you discuss your work and recent review article on surgical removal of the primary tumor in women with de novo metastatic breast cancer?

DR MORROW: We recently published an exploratory analysis evaluating surgery for patients with de novo Stage IV disease in the modern era — that is, the time since we began administering taxanes and trastuzumab for patients with HER2-positive disease. We found that the benefit of surgery in this setting was confined to patients whose disease had a specific target, either estrogen receptor or HER2 overexpression. Patients with triple-negative disease receiving conventional chemotherapy didn't benefit from surgery (Neuman 2010).

My colleague Tari King has launched a prospective, multi-institutional study (NCT00941759) that will involve collecting specimens for biomarkers in patients presenting with Stage IV disease who do or do not undergo surgery in the modern era. Currently, for patients who present with Stage IV disease and an intact primary tumor, surgery is never my first step. I administer systemic therapy initially. Patients who experience rapid disease progression

won't benefit from surgery, and administering up-front therapy prevents an unnecessary operation. For patients with low-volume metastatic disease whose disease responds, I offer surgery as an option, clarifying that we don't know for certain whether they will benefit.

Track 11

DR LOVE: What is your take on the issue of whether to treat small, node-negative, HER2-positive breast cancer?

DR MORROW: This is a difficult question. Published data report poor prognoses for patients with small, HER2-overexpressing tumors (1.2). Our data from Memorial show essentially no relapses among patients with small tumors treated with trastuzumab and chemotherapy (1.2).

Initially, I was opposed to the idea of administering a potentially toxic treatment with chemotherapy and trastuzumab to patients with T1a cancer, but I believe accumulating data indicate that you can overcome the bad biology if you treat it with targeted therapy.

1.2

Prognosis and Benefit from Trastuzumab in Patients with Small, Node-Negative, HER2-Positive Breast Cancer

Group	Study parameters	Treatment with trastuzumab	Main outcomes
European Institute of Oncology[1]	1999-2006 pT1a-b N = 150	Matched node-negative cohort; no patient received trastuzumab	5-y DFS ER+, HER2-: 99% ER+, HER2+: 92% ER-, HER2-: 92% ER-, HER2+: 91%
The University of Texas MD Anderson Cancer Center[2]	1990-2002 pT1a-b N = 965	No patient received adjuvant chemotherapy or trastuzumab	5-y RFS HER2-: 93.7% HER2+: 77.1%
Memorial Sloan-Kettering Cancer Center[3]	2002-2008 pT1a-c N = 257	Adjuvant trastuzumab (T)-treated and nontreated cohorts	3-y DRFS No adj T therapy: 95% Adj T therapy: 100%

DFS = disease-free survival; RFS = relapse-free survival; DRFS = distant recurrence-free survival

[1] Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9; [2] Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6; [3] McArthur HL et al. Breast Cancer Symposium 2009;**Abstract 228**.

Track 14

Case discussion

A 60-year-old woman with a 2.5-cm, Grade II, strongly ER- and PR-positive, HER2-negative infiltrating ductal carcinoma (IDC) and two negative sentinel nodes and a low (5) Onco*type* DX Recurrence Score

DR MORROW: This patient would probably routinely receive chemotherapy based on tumor size criteria.

I believe that this is an ideal circumstance in which to use the Onco*type* DX assay because we know from the NSABP-B-14 data that the absolute difference in 10-year risk of recurrence achieved by adding chemotherapy to tamoxifen is small — approximately five percent overall (Paik 2006).

If you then break that down by Onco*type* DX Recurrence Score, patients with low-risk scores derive no added benefit from chemotherapy, patients with intermediate-risk scores probably don't receive added benefit from chemotherapy but patients with high-risk scores receive a truly meaningful benefit between the two groups (Paik 2006; [1.3]).

This patient's preconceived notion regarding chemotherapy was that she didn't want to receive it unless she had to. We sent her tissue for Onco*type* DX analysis, and she was in the low-risk category. She was reassured and is now receiving only aromatase inhibitor therapy.

I believe that the Onco*type* DX assay helps make these types of decisions. ■

1.3

Effect of Adding Chemotherapy to Tamoxifen According to Onco*type* DX Recurrence Score (RS) for Women with ER-Positive, Node-Negative Disease

	Ten-year distant recurrence-free survival		
Risk group	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	*p*-value
Low (RS < 18)	97%	96%	0.61
Intermediate (RS = 18-30)	91%	89%	0.39
High (RS ≥ 31)	61%	88%	<0.001

Chemotherapy = MF or CMF

Paik S et al. *J Clin Oncol* 2006;24(23):3726-34.

SELECT PUBLICATIONS

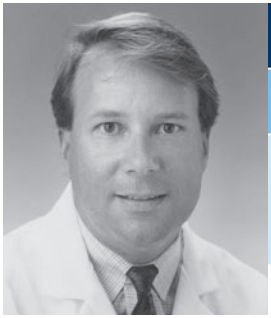
Azu M et al. **What is an adequate margin for breast-conserving surgery? Surgeon attitudes and correlates.** *Ann Surg Oncol* 2010;17(2):558-63.

Mamounas EP et al. **Association between the 21-gene Recurrence Score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** *J Clin Oncol* 2010;28(10):1677-83.

Neuman HB et al. **Stage IV breast cancer in the era of targeted therapy: Does surgery of the primary tumor matter?** *Cancer* 2010;116(5):1226-33.

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84.



INTERVIEW

Patrick I Borgen, MD

Dr Borgen is Chairman of the Department of Surgery and Director of the Brooklyn Breast Cancer Program at Maimonides Medical Center in Brooklyn, New York.

Tracks 1-10

Select Excerpts from the Interview

Track 1

DR LOVE: What are some of the most important new developments in breast cancer surgery that are being discussed?

DR BORGEN: One hot topic is total skin sparing or nipple-sparing mastectomy (NSM). An explosion of small to medium-sized series have been evaluating this procedure as the next step in cosmetic mastectomies.

I perform NSM in the setting of risk-reducing mastectomy but not for local treatment of cancer. However, recently a large (~1,000) series was published evaluating NSM in breast cancer, and the results are impressive (Petit 2009; [2.1]).

DR LOVE: What exactly is done in NSM, and what are the potential advantages?

DR BORGEN: With a small incision and the use of fiber-optic retraction, all the breast tissue is removed. Many of the major lactiferous ducts are removed from the nipple area without compromising the blood supply to the skin of the nipple. The entire envelope of the breast remains, together with a flap of the nipple skin.

One obvious benefit is the cosmetic advantage of retaining the native nipple — and elimination of the need for nipple reconstruction. Patients who have undergone NSM also report superior sensation to that experienced after conventional mastectomy.

2.1 **Efficacy and Postoperative Complications of Nipple-Sparing Mastectomy (NSM) with Intraoperative Radiation Therapy (RT) or with Delayed RT**

	NSM	NSM with intraoperative RT	NSM with delayed RT	*p*-value
N	1,001	800	201	—
Median follow-up	19 months	20 months	16 months	—
Locoregional recurrence	1.4%	1.6%	0.5%	0.22
Distal recurrence	3.6%	3.5%	4.0%	0.74
Nipple-areolar complex necrosis	3.5%	3.5%	3.5%	0.9
Nipple-areolar complex removal	5.0%	4.8%	5.4%	0.7
Local infection	2.0%	2.13%	1.49%	0.56

Petit JY et al. *Breast Cancer Res Treat* 2009;117(2):333–8.

Track 2

DR LOVE: What do you accept as an adequate surgical margin after tumor removal in breast cancer?

DR BORGEN: It varies. Margins have long been considered a surrogate for the adequacy of resection, but no trial of surgical margins has been conducted, so we must use empirical evidence.

It is important to understand that a number on a pathology report for a margin is not meaningful by itself. If the pathologist says, "You have a 1-mm margin," that could be a single focus of ductal carcinoma in situ (DCIS), which I would accept, or it could be a whole field front of DCIS, which I would not accept.

It's the volume of the disease at the edge that indicates whether tumor remains. Jay Harris conducted an analysis years ago that showed a direct correlation between the volume of resection and the chance of local recurrence (Vicini 1991). This concept makes more sense to me than a number on a pathology report.

In the case of DCIS, the ratio of the number of slides that contain DCIS to the total number of slides examined is useful. If you see DCIS on 17 out of 18 slides and a positive margin, that's not good. If it's three out of 17, that's different.

Tracks 3, 10

DR LOVE: Is there anything in the realm of sentinel lymph node biopsy that you would want to comment on?

DR BORGEN: I believe the general surgical world has accepted the fact that the breast drains as a single anatomic unit to isolated nodes. This is important because it means that whether the patient has two tumors in two quadrants or one large tumor in the breast, mapping will work and will be accurate.

DR LOVE: How many sentinel nodes should be removed?

DR BORGEN: I believe that the average should be two to three nodes. When we studied our first 10,000 sentinel node mapping procedures, we found the average to be 2.5 sentinel nodes per case. That number was constant whether we injected the tracer the day before or the morning of surgery.

When I see a case with eight or 10 sentinel nodes, that's an indication of a failed mapping procedure. In these situations the tracer may have degenerated, and I wouldn't trust sentinel node biopsy alone. Thankfully, this is becoming more rare as our nuclear medicine doctors gain more experience with the mapping procedure.

We generally use a radioactive tracer now rather than blue dye. While our rate of major reactions to blue dye is less than two percent, we have recorded no allergic reactions to the radionucleotide tracer. Furthermore, the proportion of cases in which the tracer misses a cancerous node that is discovered with blue dye is less than one to two percent.

DR LOVE: Would you comment on the controversy around the timing of sentinel node biopsy in patients receiving neoadjuvant therapy?

DR BORGEN: My bias is that I would rather perform the biopsy before therapy.

It's a fascinating issue because every group that has evaluated the accuracy of sentinel node biopsy postchemotherapy has reported a 10 percent false-negative rate. Some groups see that rate as low, and others view it as a high false-negative rate. I believe that the answer is somewhere in between. ■

SELECT PUBLICATIONS

Petit J Y et al. **Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: 1001 cases of a five years experience at the European Institute of Oncology of Milan (EIO).** *Breast Cancer Res Treat* 2009;117(2):333-8.

Vicini FA et al. **The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy.** *Ann Surg* 1991;214(3):200-4.

INTERVIEW

George W Sledge Jr, MD

Dr Sledge is Ballve-Lantero Professor of Medicine, Professor of Medicine and Pathology and Co-Director of the IUSCC Breast Cancer Research Program at Indiana University Simon Cancer Center and the Indiana University School of Medicine in Indianapolis, Indiana.

Tracks 1-17

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the randomized controlled trial from India evaluating the single-injection depot administration of progesterone prior to breast cancer surgery?

DR SLEDGE: Over the years a large number of studies have examined the timing of the menstrual cycle at the time of breast cancer surgery and any relation with prognosis. Some of these studies suggested a relationship, and it remained an interesting observation without a definite answer.

The hypothesis investigated in this trial is that if the timing of the menstrual cycle at the time of surgery indeed has a relationship with outcome, then an artificial alteration around the time of surgery could benefit patients.

The trial randomly assigned 1,000 women to progesterone versus no progesterone before surgery, and the results are surprisingly positive (Badwe 2009; [3.1]). An approximately 10 percent improvement in disease-free survival was recorded in the subpopulation with lymph node-positive disease. These results are most interesting and must be confirmed.

If these results are confirmed in another trial, this could be a simple and inexpensive intervention available to patients with breast cancer around the world.

DR LOVE: How do you think progesterone may be working in this setting?

DR SLEDGE: Large doses of progesterone could affect receptors other than estrogen receptors. Because the benefit was observed in both hormone receptor-positive and hormone receptor-negative breast cancer, it must be mediated via different growth factor receptors within the steroid receptor superfamily.

3.1

Effect of Single 500-mg Depot Hydroxyprogesterone Prior to Surgery on Disease-Free Survival (DFS) among Women with Operable Breast Cancer

	Control group (no preoperative progesterone)	Treatment group (preoperative progesterone)	*p*-value
DFS: All patients (median follow-up 65 months)	70%	74%	0.195
DFS: Lymph node-positive disease	54.6%	64.7%	0.03

Badwe RA et al. San Antonio Breast Cancer Symposium 2009;**Abstract 72**.

Track 5

DR LOVE: Would you summarize the article you coauthored on the SWOG study of prognostic and predictive value of the Onco*type* DX assay for postmenopausal patients with ER-positive, node-positive breast cancer?

DR SLEDGE: The data from SWOG-8814, which evaluated tamoxifen with or without chemotherapy for postmenopausal women with ER-positive, node-positive breast cancer, suggested that chemotherapy was beneficial for these patients (Albain 2010). After the release of the Onco*type* DX data on patients

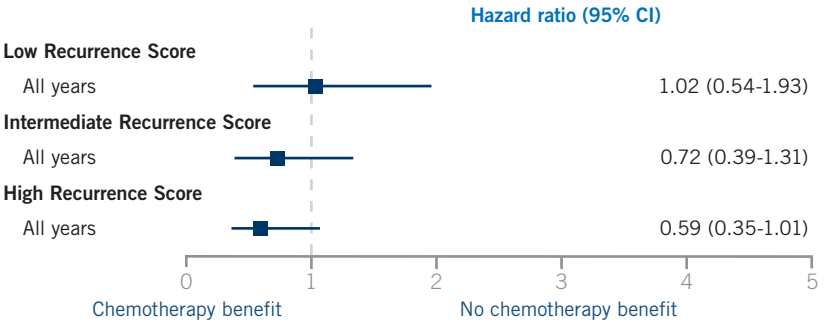
with node-negative breast cancer (Paik 2004), the obvious question was whether the same biology would apply in lymph node-positive disease.

To assess the correlation between Recurrence Score and disease-free survival in node-positive breast cancer, we conducted a retrospective analysis of SWOG-8814, and I believe the data are consistent with what was seen with the Onco*type* DX assay for patients with node-negative disease (Paik 2004).

Patients with low Recurrence Scores appear to receive less benefit from adjuvant chemotherapy, and those with high Recurrence Scores receive relatively more benefit from adjuvant chemotherapy in addition to hormonal therapy (Albain 2010; [3.2]). I view these data as part of a suite of studies with similar results across lymph node statuses and tumor sizes.

3.2

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



CI = confidence interval

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

Track 9

DR LOVE: It's been nearly five years since data from the adjuvant trastuzumab studies were first presented at ASCO. Where are we today in terms of anti-HER2 therapy in HER2-positive, early-stage breast cancer?

DR SLEDGE: Based on these trials, the three approaches available to us with trastuzumab are to use it concurrently with chemotherapy as in the NCCTG-N9831 or NSABP trials (Perez 2007), to administer it sequentially as in one arm of the N9831 trial and the European HERA trial (Smith 2007) or to use a totally nonanthracycline-based regimen as in Slamon's BCIRG 006 trial (Slamon 2009).

It's reassuring that with longer follow-up we're still seeing significant improvements in disease-free and overall survival with trastuzumab. Unfortunately, longer-term follow-up does not suggest a plateau in terms of disease-free

survival. We're still seeing evidence that patients experience recurrence later on, and we need longer-term follow-up.

One can summarize these data by saying that trastuzumab is a good agent in the adjuvant setting and we see long-term benefits with all of these approaches. At the 2009 San Antonio meeting, Edith Perez presented updated results from N9831 that suggested but did not prove that concurrent therapy is better than the sequential approach (Perez 2009).

At the same meeting, Dennis Slamon presented an update on the BCIRG trial that again suggested that both of the trastuzumab-containing arms had good long-term outcomes.

The disease-free survival curve with the anthracycline-based regimen is a little above the curve for the nonanthracycline-based regimen, and depending on your perspective, those differences may appear profound or they may look small (Slamon 2009; [3.3]).

3.3

BCIRG 006: Disease-Free and Overall Survival among Patients with HER2-Positive Early Breast Cancer Treated with Docetaxel, Carboplatin and Trastuzumab (TCH), AC Followed by Docetaxel (AC → T) or AC Followed by Docetaxel and Trastuzumab (AC → TH) — 65-Month Median Follow-Up

	N	Events	*p*-value	Adjusted HR (95% CI)
Disease-free survival				
AC → T	1,073	257		1 (reference)
AC → TH	1,074	185	<0.001	0.64 (0.53-0.78)
TCH	1,075	214	0.04	0.75 (0.63-0.90)
Overall survival				
AC → T	1,073	141		1 (reference)
AC → TH	1,074	94	<0.001	0.63 (0.48-0.81)
TCH	1,075	113	0.038	0.77 (0.60-0.99)

HR = hazard ratio; CI = confidence interval

Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2009;**Abstract 62**.

Track 17

DR LOVE: Would you comment on Joyce O'Shaughnessy's data from the randomized Phase II trial of the PARP inhibitor BSI-201 for patients with triple-negative metastatic breast cancer?

DR SLEDGE: The data from this study were striking (O'Shaughnessy 2009; [3.4]). Even though it was a randomized Phase II trial, it showed an overall survival advantage. That quickly led to the development of a large randomized Phase III trial that started in June 2009, within weeks of the ASCO meeting, which has already closed to accrual.

I'm not certain I've seen a Phase III metastatic proof-of-concept trial open and close in eight months before. It's fascinating. If this trial is positive, I believe that it will move this agent into clinical trials in the adjuvant setting posthaste. ■

3.4

Phase II Randomized Trial of Gemcitabine/Carboplatin (GC) with or without BSI-201 — a PARP1 Inhibitor — for Triple-Negative Metastatic Breast Cancer Previously Treated with Zero to Two Chemotherapy Regimens

	GC	GC + BSI-201	Hazard ratio (95% CI)	*p*-value
Objective response rate (n = 44, 42)	16%	48%	—	0.002
Median progression-free survival (n = 59, 57)	3.3 mo	6.9 mo	0.342 (0.200-0.584)	<0.0001
Median overall survival (n = 59, 57)	7.7 mo	12.2 mo	0.50 (0.30-0.82)	0.005

CI = confidence interval

O'Shaughnessy J et al. San Antonio Breast Cancer Symposium 2009;**Abstract 3122**.

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.

Albain KS et al. **Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: A phase 3, open-label, randomised controlled trial.** *Lancet* 2009;374(9707):2055-63.

Badwe RA et al. **Single injection depot progesterone prior to surgery and survival in women with operable breast cancer: A randomized controlled trial.** San Antonio Breast Cancer Symposium 2009;**Abstract 72**.

O'Shaughnessy J et al. **Final results of a randomized Phase II study demonstrating efficacy and safety of BSI-201, a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with gemcitabine/carboplatin (G/C) in metastatic triple negative breast cancer (TNBC).** San Antonio Breast Cancer Symposium 2009;**Abstract 3122**.

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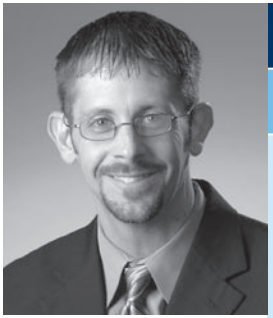

INTERVIEW

Bryan P Schneider, MD

Dr Schneider is Assistant Professor of Medicine in the Divisions of Hematology/Oncology and Clinical Pharmacology in the Departments of Medicine and Medical/Molecular Genetics at the Indiana University Melvin and Bren Simon Cancer Center in Indianapolis, Indiana.

Tracks 1-7

Select Excerpts from the Interview

Track 3

DR LOVE: What are your thoughts on the Onco*type* DX assay for patients with node-positive tumors (Albain 2010; [3.2])?

DR SCHNEIDER: Patients with low-risk Recurrence Scores did not gain substantial benefit from the addition of chemotherapy. This suggested that subgroups of patients with node-positive disease may not need chemotherapy. The problem is that the risk of relapse was substantially high, even in the low-risk category. This strategy could be valuable for those with minimal lymph node positivity and comorbid conditions that warrant the avoidance of chemotherapy.

DR LOVE: How do you feel about surgeons ordering Onco*type* DX?

DR SCHNEIDER: Our surgeons frequently talk to our patients about the Onco*type* DX assay. It's convenient when I meet the patient after surgery and they already have a Recurrence Score. The caveat is that we believe enrollment in TAILORx is important, so I ask our surgeons to discuss the TAILORx trial before they suggest the Onco*type* DX assay.

Track 7

DR LOVE: What are the current major adjuvant trials for patients with HER2-positive early breast cancer?

DR SCHNEIDER: ALTTO is an adjuvant trial attempting to improve on HER2 blockade (4.1). The trial randomly assigns patients to a control arm, which is trastuzumab for one year, standard chemotherapy with trastuzumab followed by lapatinib, trastuzumab and lapatinib or lapatinib alone.

Lapatinib blocks HER2 in a slightly different way than trastuzumab does. Lapatinib is a small-molecule tyrosine kinase inhibitor that blocks both HER1 and HER2. The BETH trial is evaluating chemotherapy/trastuzumab with or without bevacizumab (4.1).

The idea is to possibly capture a population that stands to benefit from dual blockade. Many HER2-positive tumors overexpress VEGF, a known target for bevacizumab. ■

4.1

Ongoing Adjuvant Phase III Trials for Patients with HER2-Positive Early Breast Cancer

Protocol	No. of patients	Eligibility	Randomization arms
ALTTO	8,000	→ HER2+ → At least 4 cycles of (neo)adjuvant chemotherapy prior to surgery	→ **H** q3wk x 52 wk → **L** daily x 52 wk → **H** qwk x 12 → 6-wk washout → **L** daily x 34 wk → [**L** daily + **H** q3wk] x 52 wk
BETH	3,500	→ HER2+ central FISH → Node+ or high-risk node-negative	→ **TCH*** or (**TH** → **FEC**†) → **H** to complete 1 y → **TCHB*** or (**THB** → **FEC**†) → **HB** to complete 1 y

H = trastuzumab; L = lapatinib; T = docetaxel; C = carboplatin; F = 5-FU; E = epirubicin; C† = cyclophosphamide; B = bevacizumab; * Chemotherapy used by NSABP/CIRG investigators (Cohort 1); † Chemotherapy used by independent investigators (Cohort 2)

NCI Physician Data Query, April 2010; **www.breastinternationalgroup.org**; **www.alttotrials.com**.

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.

Albain KS et al. **Prediction of adjuvant chemotherapy benefit in endocrine responsive, early breast cancer using multigene assays.** *Breast* 2009;18(3):S141-5.

Rayhanabad JA et al. **Changing paradigms in breast cancer management: Introducing molecular genetics into the treatment algorithm.** *Am Surg* 2008;74(10):887-90.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Analysis of the association between Onco*type* DX Recurrence Score (RS) and risk of locoregional recurrence among patients with ER-positive, node-negative breast cancer indicated that for patients with low-risk scores, the addition of tamoxifen substantially decreased the risk of local recurrence.**
   a. True
   b. False

2. **Analysis of the association between Onco*type* DX RS and risk of locoregional recurrence among patients with ER-positive, node-negative breast cancer indicated that for patients with high-risk scores, the addition of tamoxifen to chemotherapy reduced the 10-year locoregional recurrence rate by approximately _____ compared to placebo.**
   a. Two percent
   b. Five percent
   c. 10 percent
   d. 20 percent

3. **The Onco*type* DX RS predicts benefit or lack of benefit from chemotherapy for postmenopausal patients with ER/PR-positive, node-negative early breast cancer.**
   a. True
   b. False

4. **In the retrospective analysis published by Albain and colleagues evaluating the Onco*type* DX assay for women with ER-positive, node-positive breast cancer who received adjuvant tamoxifen with or without chemotherapy, the RS _____ prognostic for patients with positive nodes.**
   a. Was
   b. Was not

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

6. **Longer-term follow-up of patients with HER2-positive breast cancer treated with chemotherapy/trastuzumab demonstrates a plateau for disease-free survival, suggesting that patients who received treatment are not at risk for disease recurrence.**
   a. True
   b. False

7. **The addition of BSI-201 to gemcitabine/carboplatin _____ significantly improve overall survival for patients with triple-negative metastatic breast cancer.**
   a. Did
   b. Did not

8. **In the TAILORx study, patients with an Onco*type* DX RS of _____ will be randomly assigned to treatment with chemotherapy followed by hormonal therapy or hormonal therapy alone.**
   a. Lower than 11
   b. 11 to 25
   c. Higher than 25
   d. Both a and b

9. **An ongoing adjuvant chemotherapy trial for patients with HER2-positive early breast cancer called _____ is studying the use of lapatinib with or without trastuzumab.**
   a. TAILORx
   b. ALTTO
   c. BETH
   d. Both a and c

10. **Data from a retrospective analysis of a SWOG trial suggested that patients with node-positive disease and a low-risk Onco*type* DX RS might not benefit substantially from chemotherapy.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update for Surgeons — Issue 1, 2010

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
Prognostic and predictive value of the Onco*type* DX Recurrence Score for postmenopausal patients with node-negative and node-positive early breast cancer (BC)	4 3 2 1	4 3 2 1
Ongoing, prospective clinical trials of the Onco*type* DX assay in early BC	4 3 2 1	4 3 2 1
Quality control in the assessment of ER and HER2 status	4 3 2 1	4 3 2 1
Relationship between routine pretreatment MRI and mastectomy rate, margin status and local control	4 3 2 1	4 3 2 1
Update on adjuvant chemotherapy/trastuzumab for HER2-positive early BC and ongoing second-generation trials of adjuvant anti-HER2 therapy	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:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ 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:

- Utilize genomic assays to quantify recurrence risk and aid in individualized recommendations for systemic therapy for postmenopausal patients with ER-positive, node-negative or node-positive breast cancer . . . . . 4 3 2 1 N/M N/A
- Evaluate issues related to the accuracy, reliability and interpretation of the ER and HER2 status of breast tumors in the context of local laboratory practices and national guidelines . . . . . 4 3 2 1 N/M N/A
- Consider emerging data for sentinel lymph node evaluation and complete axillary dissection for documented micrometastases in surgical practice. . . . . 4 3 2 1 N/M N/A
- Assess the clinical utility of preoperative magnetic resonance imaging for breast cancer detection and diagnosis . . . . . 4 3 2 1 N/M N/A
- Identify patients with DCIS who may benefit from surgical resection without radiation therapy . . . . . 4 3 2 1 N/M N/A
- Evaluate the risks and benefits of partial breast irradiation. . . . . 4 3 2 1 N/M N/A
- Summarize the emerging data on select novel therapeutic agents or regimens in the treatment of early and metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Describe current approaches and ongoing clinical trials addressing the treatment of HER2-positive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the option of participating in ongoing clinical trials . . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

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
Monica Morrow, MD	4 3 2 1	4 3 2 1
Patrick I Borgen, MD	4 3 2 1	4 3 2 1
George W Sledge Jr, MD	4 3 2 1	4 3 2 1
Bryan P Schneider, 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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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

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 CME.ResearchToPractice.com.

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Breast Cancer® UPDATE

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