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Breast Cancer® UPDATE

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

EDITOR

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INTERVIEWS

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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 trials lead to the continual emergence of new therapeutic agents, treatment strategies and diagnostic/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 and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Appraise the potential utility of genomic assays to aid in the quantification of risk and selection of individualized treatment for select patients with node-positive breast cancer.
- Assimilate new clinical trial evidence into the therapeutic algorithm for localized and advanced, ER-positive, pre- and postmenopausal breast cancer.
- Formulate an evidence-based algorithm for the management of HER2-positive, localized or previously treated metastatic breast cancer.
- Communicate the efficacy and safety of various chemotherapy regimens in combination with bevacizumab to patients with HER2-negative metastatic breast cancer who may be eligible for anti-angiogenic treatment.
- Devise a treatment algorithm for patients with locally advanced or metastatic, triple-negative breast cancer, incorporating chemotherapy, novel molecular-targeted agents and clinical trial participation, when appropriate.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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CONTENT VALIDATION AND DISCLOSURES

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INTERVIEW

Ian E Smith, MD

Prof Smith is Professor of Cancer Medicine in the Department of Medicine at The Royal Marsden Hospital in London, United Kingdom.

Tracks 1-17

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the BIG 1-98 trial and the new analysis adjusting for treatment crossover?

PROF SMITH: When the initial BIG 1-98 results reported a benefit for letrozole compared to tamoxifen, women receiving tamoxifen were allowed to cross over to letrozole for ethical reasons, and approximately 25 percent did so.

One of the interesting reports from the 2009 San Antonio meeting was a statistical analysis of the BIG 1-98 data that attempted to take into account the crossover effect. A clear survival benefit was reported with this analysis, which is interesting because it's the first time that a survival benefit has been shown for front-line adjuvant aromatase inhibitor therapy (Regan 2009; [1.1]).

1.1

BIG 1-98: Adjuvant Letrozole (Let) versus Tamoxifen (Tam) for Postmenopausal Women with ER-Positive Breast Cancer

	Events		
	Let (n = 2,463)	Tam (n = 2,459)	Hazard ratio* (95% CI)
Disease-free survival			
ITT population	509	565	0.88 (0.78-0.99)
Censored			0.84 (0.74-0.95)
IPCW†			0.85 (0.76-0.96)
Overall survival			
ITT population	303	343	0.87 (0.75-1.02)
Censored			0.81 (0.69-0.94)
IPCW†			0.83 (0.71-0.97)
Time to distance recurrence			
ITT population	257	298	0.85 (0.72-1.00)
Censored			0.81 (0.68-0.96)
IPCW†			0.81 (0.69-0.96)

* Hazard ratio < 1.0 favors Let

† IPCW, the inverse probability of censor weighting, to handle induced selection bias by artificial censoring at crossover, is used to estimate the treatment effect. IPCW assigns a weight to each patient who remains on Tam so that she accounts in the analysis not only for herself but also for those with similar characteristics who are artificially censored at crossover to Let.

"The selective crossover affects efficacy results of the ITT analysis of the BIG 1-98 monotherapy comparison. Additional IPCW analysis accounting for the selective crossover indicates that the benefit of Let over Tam is greater than that reflected by the ITT estimate. Let for 5yrs is significantly better than Tam for DFS and OS."

Regan MM et al. San Antonio Breast Cancer Symposium 2009;**Abstract 16**.

Track 4

DR LOVE: Would you discuss the outcome analysis in premenopausal patients at diagnosis in the MA17 trial of extended adjuvant aromatase inhibitor therapy, which was presented at SABCS 2009?

PROF SMITH: The MA17 trial was probably the most important of all the aromatase inhibitor trials because it showed that if you've been receiving five years of tamoxifen and your disease is in remission, switching to an aromatase

inhibitor decreases your risk of recurrence even if you're in a good prognosis group.

Now it is standard practice, particularly for patients at higher risk, to move on to receiving letrozole after five years of tamoxifen. These results continue to improve with longer follow-up. In the MA17 trial, the longer the patients receive letrozole, the better they seem to fare.

The new analysis presented at San Antonio by Paul Goss studied the subset of patients who were premenopausal at the initiation of tamoxifen therapy but in whom subsequent menopause had occurred by the end of the five years of tamoxifen therapy, whether it is biological or from oophorectomy or chemotherapy-induced ovarian suppression.

Dr Goss reported that this group also gained from receiving letrozole after tamoxifen, and the benefit was large — approximately a seven percent overall disease-free survival (DFS) improvement. In patients with node-negative disease, the DFS benefit was 11 percent (Goss 2009; [1.2]), which was rather surprising.

Although women who were premenopausal at the start of tamoxifen therapy were at higher risk of relapse afterward, none of the premenopausal women with node-negative disease who have continued on to letrozole have experienced a relapse so far (1.2), which is quite interesting.

1.2

Outcomes of Women Who Were Premenopausal at Diagnosis of Breast Cancer in the MA17 Trial of Extended Adjuvant Aromatase Inhibitor Therapy

	Premenopausal n = 889	Postmenopausal n = 4,277
Four-year disease-free survival*		
All patients	10.1% HR = 0.25; $p < 0.0001$	3.3% HR = 0.69; $p = 0.0008$
Node-positive	9.6% HR = 0.37; $p = 0.008$	7.0% HR = 0.68; $p = 0.03$
Node-negative	11.5% HR = 0.00; $p = 0.005$	1.1% HR = 0.58; $p = 0.04$
Interaction between treatment benefit and menopausal status (pre vs post)	HR = 0.39; $p = 0.02$	

* Percent difference for patients receiving letrozole versus placebo after five years of tamoxifen treatment

"Letrozole after tamoxifen was more effective in improving DFS in women who were premenopausal at primary diagnosis than those who were postmenopausal. Letrozole was well tolerated in premenopausal women.

These data indicate that women who are premenopausal at the time of diagnosis but become postmenopausal anytime before, or during, adjuvant tamoxifen should be considered for extended adjuvant therapy with letrozole."

Goss PE et al. San Antonio Breast Cancer Symposium 2009;**Abstract 13**.

Track 12

DR LOVE: What are your thoughts on the plenary presentation at ASCO 2009 by Joyce O'Shaughnessy on the efficacy of the PARP inhibitor BSI-201 in patients with metastatic triple-negative breast cancer (TNBC)?

PROF SMITH: This study evaluated carboplatin/gemcitabine with versus without a PARP inhibitor for patients with TNBC. The authors reported a strikingly superior benefit with the addition of the PARP inhibitor to chemotherapy (O'Shaughnessy 2009; [1.3]). A survival benefit was also evident, which is unusual in metastatic breast cancer. In fact, the last time we saw a similar survival benefit was with trastuzumab. A great deal of excitement surrounds this finding.

1.3 **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

Conclusions: Updated results at SABCS 2009

- Median PARP1 expression was significantly higher in triple-negative breast cancer, compared to normal breast tissue, confirming earlier observations.
- BSI-201 was well tolerated and neither contributed to new toxicities nor potentiated known toxicities of GC alone.
- This updated analysis demonstrates that BSI-201 in combination with GC significantly improves overall survival compared to GC alone.

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

Track 15

DR LOVE: Another interesting new agent is T-DM1, the trastuzumab/maytansine conjugate in patients with metastatic HER2-positive disease. What are your thoughts on the emerging data with this agent?

PROF SMITH: T-DM1 is a great agent. I was involved in a Phase I trial evaluating maytansine, and it was toxic. Now, by tagging maytansine and conjugating it with trastuzumab, it's internalized. It's targeted to the HER2-positive cells, and it's clearly active. Not only that, but patients also experience little toxicity with T-DM1 (Krop 2009; Vogel 2009).

DR LOVE: What do you think we'd see if we evaluated agents such as lapatinib or pertuzumab in combination with T-DM1 (1.4)?

PROF SMITH: An ongoing trial that I find attractive is evaluating T-DM1 with pertuzumab, which is another monoclonal antibody that attacks a different part of the external domain of the HER2 receptor. Pertuzumab disrupts the formation of HER2:HER1 and HER2:HER3 heterodimers, which is how the intracellular signaling process is activated. Data indicate that trastuzumab combined with pertuzumab may be more effective than trastuzumab alone (Gelmon 2008).

T-DM1 will probably prove to be better than trastuzumab because evidence indicates that T-DM1 is active after failure on prior anti-HER2 therapy (Krop 2009). Thus, T-DM1 and pertuzumab seem to me to be a fantastically promising combination, as does the T-DM1/lapatinib combination. ■

1.4

Ongoing Trials for Patients with HER2-Positive Locally Advanced Breast Cancer (LABC) or Metastatic Breast Cancer (mBC) Evaluating T-DM1-Based Therapy After Disease Progression on Trastuzumab-Based Therapy

Protocol ID	Phase	Target accrual	Eligibility	Randomization/ treatment
TDM4370g	III	580	HER2-positive LABC or mBC	T-DM1 vs L + C
TDM4373g	Ib/II	60	HER2-positive LABC or mBC	T-DM1 + pertuzumab
TDM4688g	II	50	HER2-positive LABC or mBC*	T-DM1 + pertuzumab

L = lapatinib; C = capecitabine
* After disease progression on T-DM1 alone

NCI Physician Data Query, January 2010; **www.clinicaltrials.gov**.

SELECT PUBLICATIONS

Gelmon K et al. **Results of a phase II trial of trastuzumab (H) and pertuzumab (P) in patients (pts) with HER2-positive metastatic breast cancer (MBC) who had progressed during trastuzumab therapy.** *Proc ASCO* 2008;**Abstract 1026**.

Goss PE et al. **Outcomes of women who were premenopausal at diagnosis of early stage breast cancer in the NCIC CTG MA17 trial.** San Antonio Breast Cancer Symposium 2009;**Abstract 13**.

Krop I et al. **A Phase II study of trastuzumab-DM1 (T-DM1), a novel HER2 antibody-drug conjugate, in patients previously treated with lapatinib, trastuzumab, and chemotherapy.** San Antonio Breast Cancer Symposium 2009;**Abstract 5090**.

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**.

Regan MM et al. **Adjusting for selective crossover in analyses of letrozole (Let) versus tamoxifen (Tam) in the BIG 1-98 trial.** San Antonio Breast Cancer Symposium 2009;**Abstract 16**.

Vogel CL et al. **A phase II study of trastuzumab-DM1 (T-DM1), a HER2 antibody-drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (MBC): Final results.** *Proc ASCO* 2009;**Abstract 1017**.

INTERVIEW

John F R Robertson, MB, ChB, BSc, MD

Prof Robertson is Professor of Surgery and Head of the Academic Division of Breast Surgery at Nottingham City Hospital in Nottingham, United Kingdom.

Tracks 1-10

Track 1	Current clinical research strategies for fulvestrant in postmenopausal patients with ER-positive mBC
Track 2	FACT trial: First-line anastrozole with or without fulvestrant for postmenopausal patients with ER-positive mBC
Track 3	Biomarker changes after presurgical fulvestrant 500 mg with anastrozole, fulvestrant 500 mg or anastrozole in postmenopausal patients with ER-positive early BC
Track 4	FIRST trial of fulvestrant 500 mg versus anastrozole for postmenopausal patients with ER-positive mBC
Track 5	CONFIRM trial: Improvement in time to disease progression with high-dose versus standard-dose fulvestrant
Track 6	Rationale for a clinical trial of adjuvant fulvestrant
Track 7	Activity of fulvestrant in patients with heavily pretreated HER2-positive mBC
Track 8	Implications of recent fulvestrant data for the development of next-generation clinical trials
Track 9	POETIC (PeriOperative Endocrine Therapy — Individualized Care) trial
Track 10	Use of adjuvant fulvestrant off protocol

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you summarize the findings and implications of the recent trials evaluating fulvestrant in the treatment of hormone receptor-positive breast cancer?

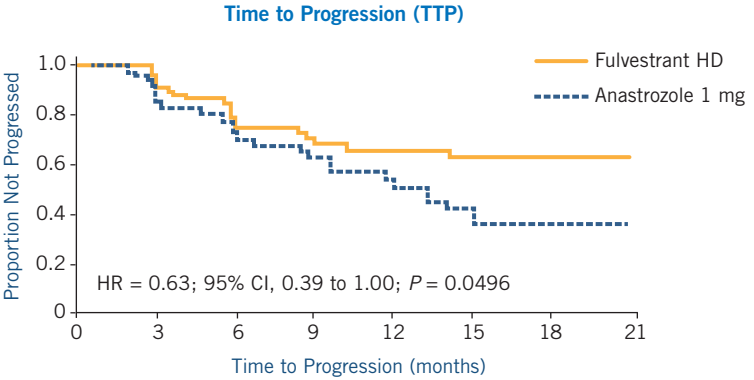
PROF ROBERTSON: We have data from three consecutives studies — FACT, FIRST and CONFIRM — that I believe provide support for further development of this agent.

In 2008 we presented data from the randomized Phase II FIRST study, which evaluated fulvestrant 500 mg monthly with a 500-mg loading dose on day 14 of the first cycle versus anastrozole as first-line treatment for advanced breast cancer, which showed fulvestrant to be better (Ellis 2008; Robertson 2009a; [2.1]).

Based on what was presented in 2009, I believe that we should focus more attention on fulvestrant. Data were presented on two different strategies — the high-dose approach and the attempt to reduce the competing ligand, estradiol, by administering an aromatase inhibitor along with fulvestrant in the FACT trial. FACT evaluated anastrozole with or without fulvestrant 250 mg monthly with a loading dose, in the first-line setting, and it was a negative study (Bergh 2009). No difference was detected between the two treatments.

2.1

FIRST: Fulvestrant 500 mg versus Anastrozole for ER-Positive Advanced Breast Cancer



Anastrozole median TTP: 12.5 months
Fulvestrant HD median TTP: Not reached

Robertson JF et al. *J Clin Oncol* 2009a;27(27):4530-5.

Tracks 3-4

DR LOVE: Would you discuss your biomarker study evaluating preoperative fulvestrant and anastrozole?

PROF ROBERTSON: We evaluated high-dose fulvestrant, 500 mg, versus high-dose fulvestrant with anastrozole versus anastrozole alone. Fulvestrant, or the placebo, was administered on day 1 and anastrozole, or placebo, was administered daily for 14 to 21 days. Surgery was performed between days 15 and 22. The trial was randomized with 40 patients per arm, and we examined the pre- and post-treatment data for ER, PgR and Ki-67.

We found that the ER was significantly reduced from baseline in each of the three treatment groups, which was not reported previously. In addition, we saw highly significant differences among the groups. The two treatments with fulvestrant resulted in significantly greater downregulation of ER than did anastrozole alone (Robertson 2009b).

The other important point is that the combination therapy was no better than fulvestrant alone. So, although both arms containing fulvestrant were better than the aromatase inhibitor alone, the combination did not add to fulvestrant, which is in keeping with the FACT trial data.

It could be that the advantage in higher-dose fulvestrant has to do with acquired resistance, not the initial response. In the FIRST trial — comparing first-line fulvestrant 500 mg to anastrozole — although time to disease progression was significantly prolonged in favor of high-dose fulvestrant, the time to progression (TTP) curves didn't separate until after the first six months (Robertson 2009a; [2.1]).

With the 500-mg dose of fulvestrant, we've reduced the ER even further than we do with an aromatase inhibitor, and with the downregulation of ER we may not obtain the cross talk that allows the development of breast cancer resistance to endocrine therapies.

Tracks 5-6

DR LOVE: Can you comment on the implications of the CONFIRM data?

PROF ROBERTSON: This was a Phase III trial comparing fulvestrant 250 mg monthly to 500 mg monthly with a loading dose in more than 700 patients. They could have experienced disease progression in the adjuvant or advanced setting, and roughly 50 percent had previously received an aromatase inhibitor. The other 50 percent had received an antiestrogen agent. That's an important point because the results appear to be equally applicable to both subgroups.

The data showed a highly significant difference in TTP favoring the high-dose strategy (Di Leo 2009; [2.2]). I can't recall another second-line Phase III randomized study of an endocrine therapy compared to the standard in which we saw a significant difference in TTP in the first analysis. They also observed that the survival curves start to separate, although they're not significant. That, too, is unusual.

The safety data showed that despite doubling the dose, no increase in side effects occurred. In addition, because the TTP curve is longer, patients were receiving the 500-mg dose longer, and the side-effect profile was the same.

DR LOVE: Do you believe that these data are statistically significant enough to warrant evaluating fulvestrant in the adjuvant setting?

PROF ROBERTSON: Yes, I believe that we should conduct an adjuvant trial with fulvestrant. Sentiments are mixed in response to these data. Those who understand the field and realize that these are unusual data are excited. Some believe that we've known about fulvestrant for a long time and are less excited about the data. However, I suspect that if you attached a different name to the drug, physicians would be excited about it.

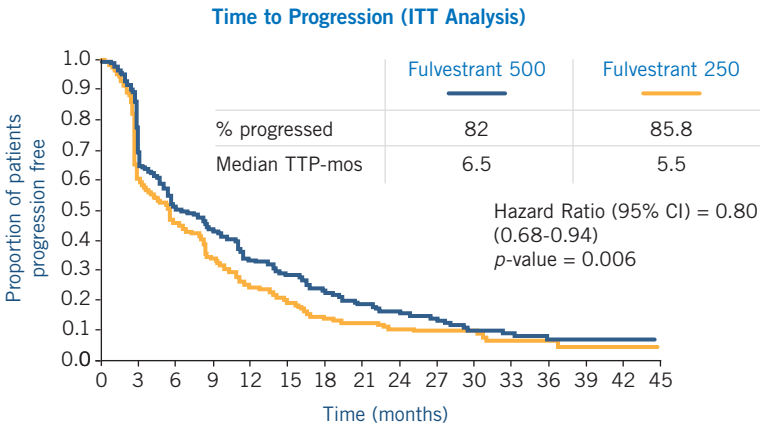
DR LOVE: What design would you consider for an adjuvant trial with fulvestrant?

PROF ROBERTSON: One of the problems with conducting adjuvant clinical trials in postmenopausal patients with ER-positive breast cancer is that most of the tumors are small and of a lower grade, so the number of events is small. I believe that we should focus on a higher-risk, node-positive population.

One clinical trial strategy that could be used is a crossover approach with two to three years of an aromatase inhibitor followed by high-dose fulvestrant. Another strategy would be extended adjuvant therapy, such as in MA17, with a crossover at five years from letrozole to fulvestrant or placebo. Both of those options would be attractive for an adjuvant clinical trial with fulvestrant. ■

2.2

CONFIRM: Fulvestrant 250 mg versus 500 mg in ER-Positive Breast Cancer Failing on Prior Endocrine Therapy



With permission from Di Leo A et al. San Antonio Breast Cancer Symposium 2009;**Abstract 25**.

SELECT PUBLICATIONS

Bergh J et al. **First results from FACT — An open-label, randomized phase III study investigating loading dose of fulvestrant combined with anastrozole versus anastrozole at first relapse in hormone receptor positive breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 23**.

Di Leo A et al. **CONFIRM: A Phase III, randomized, parallel-group trial comparing fulvestrant 250 mg vs fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 25**.

Ellis MJ et al. **A comparison of high-dose (HD, 500 mg) fulvestrant vs anastrozole (1 mg) as first-line treatments for advanced breast cancer: Results from FIRST.** San Antonio Breast Cancer Symposium 2008;**Abstract 6126**.

Robertson JF et al. **Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the FIRST study.** *J Clin Oncol* 2009a;27(27):4530-5.

Robertson JFR et al. **Tumor biomarker changes following pre-surgical treatment with 500 mg fulvestrant plus anastrozole versus 500 mg fulvestrant alone and 1 mg anastrozole alone.** San Antonio Breast Cancer Symposium 2009b;**Abstract 24**.

INTERVIEW

Michael Untch, MD, PhD

Prof Untch is Head of the Clinic for Gynecology, Gynecologic Oncology and Obstetrics and Head of the Breast Cancer Center, HELIOS Klinikum Berlin-Buch at the Academic Hospital of the University Charité in Berlin, Germany.

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the data evaluating concurrent versus sequential trastuzumab/chemotherapy in the adjuvant setting?

PROF UNTCH: Perez and colleagues have shown that the concomitant administration of adjuvant chemotherapy with trastuzumab resulted in a better disease-free survival than administering chemotherapy first followed by

trastuzumab (Perez 2009; [3.1]). In a sort of transatlantic dialogue, debate emerged whether our European HERA design was acceptable because we administered chemotherapy first followed by trastuzumab.

In contrast, the more aggressive idea from our North American colleagues was to administer chemotherapy with trastuzumab at the beginning. So the United States trials evaluated the use of an anthracycline followed by trastuzumab, administered concurrently with a taxane.

3.1

NCCTG-N9831: Disease-Free and Overall Survival of Sequential or Concurrent Adjuvant Chemotherapy and Trastuzumab in Patients with HER2-Positive Breast Cancer (>5-Year Median Follow-Up)

Sequential versus concurrent H	N	Events	*p*-value	Adjusted HR (95% CI)
Disease-free survival				
AC → T → H versus AC → T + H → H	1,903	312	0.0190	0.75 (0.60-0.94)
Overall survival				
AC → T → H versus AC → T + H → H	1,903	168	0.135	0.79 (0.59-1.08)

HR < 1.0 favors concurrent administration of chemotherapy/trastuzumab
H = trastuzumab; A = doxorubicin; C = cyclophosphamide; T = paclitaxel

Perez EA et al. San Antonio Breast Cancer Symposium 2009;**Abstract 80**.

Track 10

DR LOVE: Would you comment on the von Minckwitz study, which evaluated the continuation of treatment with trastuzumab in patients with disease progression during trastuzumab therapy (von Minckwitz 2009)?

PROF UNTCH: Eligible patients who previously received chemotherapy and trastuzumab and were not responding or experienced recurrence were randomly assigned to trastuzumab in combination with capecitabine versus capecitabine alone.

The combination of trastuzumab/capecitabine was better in terms of time to disease progression — 8.2 months — compared to capecitabine alone at 5.6 months, with a hazard ratio of 0.69. The proof of principle was that, yes, treatment beyond disease progression is beneficial.

The trial was stopped prematurely when the data from the lapatinib study (Geyer 2006) became available. Similar results were observed with the combination of lapatinib and trastuzumab in patients with heavily pretreated metastatic breast cancer and disease progression during trastuzumab treatment (Blackwell 2009; [3.2]).

3.2

Lapatinib (L) with or without Trastuzumab (T) for Patients with Heavily Pretreated Metastatic Breast Cancer Who Experience Disease Progression While Receiving Trastuzumab-Containing Therapy

Parameter	L (n = 145)	L + T (n = 146)	Hazard ratio	*p*-value
Median progression-free survival	8.1 wk	12.0 wk	0.73	0.008
Median overall survival	9.5 mo	14.0 mo	0.74	0.026

Hazard ratio < 1.0 favors L + T

"Survival benefit was seen in the setting of 77 (52%) patients assigned to the single agent lapatinib arm undergoing a planned cross over to combination therapy at the time of progression."

Blackwell KL et al. San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

Track 11

DR LOVE: Outside of a protocol setting, how do you treat recurrent or progressive disease while administering trastuzumab?

PROF UNTCH: If a patient develops resistance after long-term treatment with trastuzumab, I switch to another chemotherapy but keep trastuzumab in the system. I switch to a combination of lapatinib and capecitabine if the patient received the chemotherapy/trastuzumab combination for a short time or if she responded initially and developed resistance after three to six months of trastuzumab.

Another scenario, which is beginning to occur more frequently, involves the patient whose disease recurs at a certain time after adjuvant therapy with trastuzumab. According to the German Guideline Commission, of which I'm a member, the approach is pragmatic. If disease recurs within six months of adjuvant therapy with trastuzumab, the patient receives capecitabine and lapatinib. If disease recurs more than two years after completion of adjuvant trastuzumab, we administer trastuzumab and capecitabine. ■

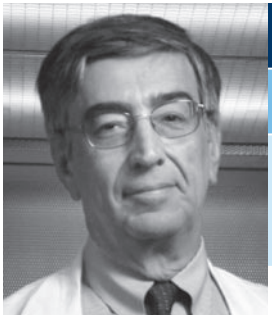
SELECT PUBLICATIONS

Blackwell KL et al. **Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy.** San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355:2733-43.

Perez EA et al. **Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial.** San Antonio Breast Cancer Symposium 2009;**Abstract 80**.

Von Minckwitz G et al. **Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03-05 study.** *J Clin Oncol* 2009;27(12):1999-2006.



INTERVIEW

Luca Gianni, MD

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

Tracks 1-9

Track 1 Perspective on the utility of prognostic and predictive genomic assays in BC

Track 2 Reliability of testing for classic pathologic biomarkers: Ki-67, ER/PR and HER2

Track 3 Cost effectiveness of the Onco*type* DX® assay

Track 4 Role of the Onco*type* DX assay for patients with node-positive BC

Track 5 Fondazione Michelangelo study of adjuvant systemic therapy for patients with node-positive, HER2-negative BC who are assigned to treatment based on risk definition assessed with the Onco*type* DX assay

Track 6 Comparison of the Onco*type* DX and MammaPrint® assays

Track 7 Association between pathologic complete response to neoadjuvant chemotherapy and Onco*type* DX Recurrence Score® in locally advanced BC

Track 8 Rationale for combined monoclonal antibody therapy with trastuzumab and pertuzumab in HER2-positive BC

Track 9 BETH trial: Evaluating synergistic combination adjuvant therapy with trastuzumab and bevacizumab in HER2-positive BC

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: What are your thoughts on the recent SWOG data set on the use of the Onco*type* DX assay in patients with node-positive disease?

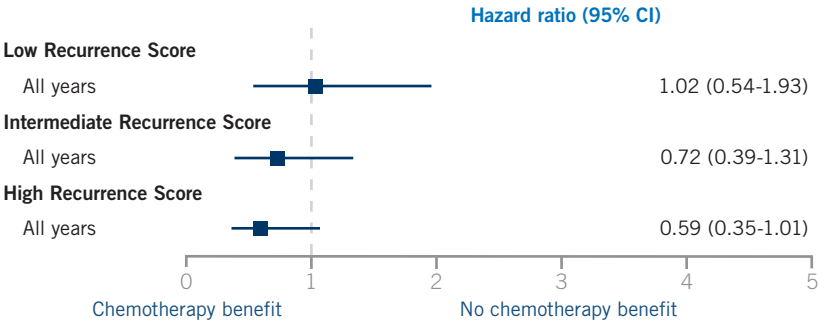
DR GIANNI: I can understand using Onco*type* in this manner. I would be somewhat reassured if the patient had a Recurrence Score of less than 18. We know that the likelihood that these patients will receive a benefit from chemotherapy is low (Albain 2010; [4.1]), and that makes the consideration of comorbidities, age and performance status more relevant. I believe that the Onco*type* DX assay can be useful for patients with node-positive disease. How useful is something we need to measure.

We have a cooperative group in Europe known as the Michelangelo Foundation. We are proposing two parallel worldwide studies, for which I will serve as principal investigator, evaluating adjuvant systemic therapy in women with

HER2-negative breast cancer assigned to treatments based on risk definition assessed with the Onco*type* DX assay. The entry criteria indicate that patients must have positive axillary lymph nodes.

4.1

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

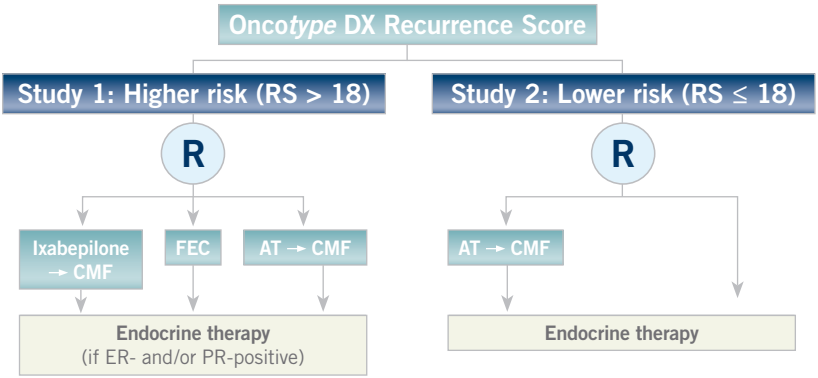


Albain KS et al. *Lancet Oncol* 2010;11(1):55–65.

One study will include patients with high or intermediate Recurrence Scores. Patients will receive experimental therapies versus classic chemotherapy. The second study will evaluate patients with low Recurrence Scores. Patients will be randomly assigned to receive chemotherapy followed by hormonal therapy versus hormonal therapy alone (4.2).

4.2

Proposed Trial Design: A Phase III Study of Adjuvant Systemic Therapy Based on Risk Definition Assessed with Onco*type* DX



Eligibility criteria: HER2-negative, node-positive breast cancer (>2 cm)

Gianni L. Personal Communication. December 2009; Gianni L. Presentation. Research To Practice Satellite Symposium, San Antonio Breast Cancer Symposium 2009; **www.fondazionemichelangelo.org**.

Track 6

DR LOVE: Would you compare and contrast the Onco*type* DX and MammaPrint assays?

DR GIANNI: The St Gallen recommendations make explicit reference to the opportunity of running tests to define the actual molecular risk in cases for which you are unsure whether you should administer chemotherapy (Goldhirsch 2009). The guidelines from the NCCN and ASCO make clear reference to the use of Onco*type* DX in such situations.

The main difference between the tests is that the MammaPrint is performed on fresh tissue. Therefore, you have to plan ahead and speak with the surgeon and pathologist so that they collect the necessary tissue. The Onco*type* DX assay has the advantage of being performed in paraffin-embedded tissue, which is the universal method of tumor tissue preservation worldwide. You always have the opportunity to retrieve a patient block and query the block for the molecular profile according to Onco*type*. That is an obvious advantage.

Track 9

DR LOVE: Would you review the second-generation adjuvant clinical trials for patients with HER2-positive breast cancer?

DR GIANNI: The two major studies are the joint CIRG- and NSABP-sponsored BETH trial, which is evaluating trastuzumab/chemotherapy with and without bevacizumab, and the ALTTO study, which is evaluating lapatinib, trastuzumab and the combination with chemotherapy.

They are completely different trials. In a way, the combination of lapatinib and trastuzumab in the ALTTO trial is aiming at the equivalent of total blockade of the HER2 receptor function, although the ALTTO study is not only that because one arm is comparing single-agent lapatinib to single-agent trastuzumab after chemotherapy.

The approach of the BETH trial is to evaluate a different question. Dr Mark Pegram and colleagues reported synergistic activity with the combination of trastuzumab and bevacizumab (Hurvitz 2009). The combination of an anti-angiogenic agent with trastuzumab achieved a level of efficacy that is comparable to the activity of chemotherapy. These observations led to the BETH trial, which is administering chemotherapy and trastuzumab with or without bevacizumab. ■

SELECT PUBLICATIONS

Goldhirsch A et al. **Thresholds for therapies: Highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009.** *Ann Oncol* 2009;20(8):1319-29.

Hurvitz SA et al. **Final results of a Phase II trial evaluating trastuzumab and bevacizumab as first line treatment of HER2-amplified advanced breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 6094**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Analysis of the adjuvant BIG 1-98 trial data adjusting for selective crossover of patients from tamoxifen to letrozole revealed no survival benefit for five years of letrozole versus five years of tamoxifen.**
   a. True
   b. False

2. **In MA17, letrozole after five years of adjuvant tamoxifen was effective at improving disease-free survival among women who were premenopausal at primary diagnosis.**
   a. True
   b. False

3. **The addition of BSI-201 to gemcitabine/carboplatin improved the _____ for patients with triple-negative metastatic breast cancer treated with zero to two prior chemotherapy regimens.**
   a. Clinical benefit rate
   b. Median progression-free survival rate
   c. Median overall survival rate
   d. Both a and b
   e. All of the above

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

5. **Patients with HER2-positive metastatic disease previously treated with HER2-directed therapies had a response rate of approximately _____ percent with T-DM1.**
   a. Five
   b. 10
   c. 30
   d. 60

6. **In the NCCTG-N9831 adjuvant trastuzumab trial, which strategy strongly trended toward an improvement in disease-free survival compared to the other strategy?**
   a. Concurrent administration of chemotherapy/trastuzumab
   b. Sequential administration of chemotherapy → trastuzumab
   c. Both strategies were equivalent with regard to disease-free survival

7. **The Phase III German study presented by von Minckwitz and colleagues demonstrated that patients with metastatic breast cancer whose disease progressed on trastuzumab benefited from continued trastuzumab in combination with chemotherapy.**
   a. True
   b. False

8. **The CONFIRM trial, which evaluated the 250-mg versus the 500-mg dose of fulvestrant in postmenopausal women with advanced breast cancer, demonstrated a statistically significant difference in time to disease progression favoring the high-dose strategy.**
   a. True
   b. False

9. **Which genomic assay requires fresh-frozen tumor specimens?**
   a. Onco*type* DX
   b. MammaPrint
   c. Both a and b
   d. Neither a nor b

10. **The BETH trial is evaluating adjuvant chemotherapy/trastuzumab with or without _____ in patients with HER2-positive breast cancer.**
    a. Lapatinib
    b. Bevacizumab
    c. T-DM1
    d. Pertuzumab

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — 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
Survival benefit for letrozole versus tamoxifen in an analysis of selective crossover in the BIG 1-98 adjuvant trial	4 3 2 1	4 3 2 1
CONFIRM: Fulvestrant 250 mg versus fulvestrant 500 mg in postmenopausal patients with ER-positive mBC	4 3 2 1	4 3 2 1
Clinical trial data supporting concurrent versus sequential chemotherapy/trastuzumab for HER2-positive early BC	4 3 2 1	4 3 2 1
Efficacy of the PARP inhibitor BSI-201 in combination with gemcitabine/carboplatin in patients with metastatic TNBC	4 3 2 1	4 3 2 1
GBG-26/BIG 3-05: Capecitabine with or without trastuzumab in patients with HER2-positive mBC progressing on trastuzumab	4 3 2 1	4 3 2 1
Fondazione Michelangelo study of adjuvant systemic therapy for women with HER2-negative BC > 2 cm assigned to treatment based on risk definition assessed with the Onco*type* DX assay	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:

- Appraise the potential utility of genomic assays to aid in the quantification of risk and selection of individualized treatment for select patients with node-positive breast cancer . . . . . 4 3 2 1 N/M N/A
- Assimilate new clinical trial evidence into the therapeutic algorithm for localized and advanced, ER-positive, pre- and postmenopausal breast cancer . . . . . 4 3 2 1 N/M N/A
- Formulate an evidence-based algorithm for the management of HER2-positive, localized or previously treated metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Communicate the efficacy and safety of various chemotherapy regimens in combination with bevacizumab to patients with HER2-negative metastatic breast cancer who may be eligible for anti-angiogenic treatment. . . . . 4 3 2 1 N/M N/A
- Devise a treatment algorithm for patients with locally advanced or metastatic, triple-negative breast cancer, incorporating chemotherapy, novel molecular-targeted agents and clinical trial participation, when appropriate. . . . . 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

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
Ian E Smith, MD	4 3 2 1	4 3 2 1
John F R Robertson, MB, ChB, BSc, MD	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
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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