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Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Ian E Smith, MD
Kathy D Miller, MD
Clifford Hudis, MD
Dennis J Slamon, MD, PhD

EDITOR

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CONTENTS

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Monograph

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Breast Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

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

LEARNING OBJECTIVES

- Use case-based learning to formulate individualized disease-management strategies for patients with breast cancer.
- Determine the utility of genomic assays in counseling patients with ductal carcinoma in situ or ER-positive early breast cancer about their risk of recurrence and the potential benefits of radiation therapy or adjuvant chemotherapy, respectively.
- Develop evidence-based treatment approaches for HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Evaluate the unique mechanisms of action and emerging clinical trial data with novel anti-HER2 agents under investigation in breast cancer.
- Recall emerging data on the role of mTOR inhibition in reversing resistance to trastuzumab and endocrine therapy in metastatic breast cancer in preparation for the potential availability of this treatment approach.
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic roles of bisphosphonates and other bone-targeted agents in disease management.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

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INTERVIEW

Ian E Smith, MD

Dr Smith is Professor of Cancer Medicine and Head of the Breast Unit at The Royal Marsden Hospital and Institute of Cancer Research in London, United Kingdom.

Tracks 1-15

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss the NEOSPHERE trial of neoadjuvant pertuzumab and trastuzumab for patients with locally advanced, inflammatory or early HER2-positive breast cancer, which was recently published in *Lancet Oncology*?

DR SMITH: The NEOSPHERE trial randomly assigned patients to 4 arms: trastuzumab/docetaxel, pertuzumab/docetaxel, trastuzumab/pertuzumab/docetaxel and trastuzumab/pertuzumab (Gianni 2012; [1.1]). The arm with the best efficacy was trastuzumab/pertu-

1.1 **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. *Lancet Oncol* 2012;13(1):25-32.

zumab/docetaxel, with about double the pathologic complete responses (pCR). What is interesting is that in the trastuzumab/pertuzumab arm, 27% of the patients with ER-negative disease experienced pCR and were probably cured with no chemotherapy.

A pCR in a patient with HER2-positive disease is usually indicative of a favorable outcome. It is unclear how predictive pCRs are in the long term, but most patients with pCRs generally fare well. In this trial, they all received chemotherapy after surgery, so we'll never really know.

This raises the question of whether we can identify markers that indicate which patients don't need chemotherapy. I believe a currently unidentifiable subgroup of patients with HER2-positive disease can be cured with combination anti-HER2 therapy alone. The trick is, can we find out who they are? A biomarker analysis of patients in the NEOSPHERE trial was presented at SABCS 2011. Unfortunately, the results were not promising (Gianni 2011).

DR LOVE: Would you also talk about the CLEOPATRA data and whether you would use pertuzumab outside of a research setting if it were available?

DR SMITH: The CLEOPATRA trial evaluated trastuzumab/docetaxel with or without the addition of pertuzumab for patients with HER2-positive metastatic breast cancer (Baselga 2012b; [1.2]). Pertuzumab made a huge difference — it extended progression-free survival by about 50%. The hazard ratio was spectacular. To put it in perspective, the benefit from adding pertuzumab to trastuzumab was as large as the original benefit of adding trastuzumab to chemotherapy. This is like another quantum leap, which is exciting.

I foresee using pertuzumab as first-line therapy in metastatic disease. I would also consider administering the combination of pertuzumab and trastuzumab for patients who experience relapse after completing adjuvant trastuzumab.

Track 8

DR LOVE: Would you comment on the recently published BOLERO-2 trial, which evaluated exemestane and everolimus in patients with ER-positive metastatic breast cancer refractory to nonsteroidal aromatase inhibitors?

1.2

CLEOPATRA Study: Efficacy and Safety of the Addition of Pertuzumab versus Placebo to Docetaxel/Trastuzumab as First-Line Therapy for Patients with HER2-Positive Metastatic Breast Cancer

Response	Pertuzumab	Placebo	Hazard ratio	*p*-value
Median PFS				
All patients (n = 402, 406)	**18.5 months**	**12.4 months**	**0.62**	**<0.001**
(Neo)adjuvant chemotherapy				
With trastuzumab (n = 47, 41)	16.9 months	10.4 months	0.62	NR
No trastuzumab (n = 137, 151)	21.6 months	12.6 months	0.60	NR
Interim OS* (n = 402, 406)	17.2%	23.6%	0.64	0.005
Complete response (n = 343, 336)	5.5%	4.2%	NR	
Partial response (n = 343, 336)	74.6%	65.2%		
Progressive disease (n = 343, 336)	3.8%	8.3%		
	Pertuzumab (n = 407)		**Placebo** (n = 397)	
Select adverse events	All grades	≥Grade 3	All grades	≥Grade 3
Febrile neutropenia	13.8%	13.8%	7.6%	7.6%
Mucosal inflammation	27.8%	NR	19.9%	NR
Diarrhea	66.8%	7.9%	46.3%	5.0%
Rash	33.7%	NR	24.2%	NR
LVSD fall; ≥10% <50%	3.8%	NR	6.6%	NR

PFS = progression-free survival; NR = not reported; OS = overall survival; LVSD = left ventricular systolic dysfunction

* Not significant because analysis did not meet O'Brien-Fleming stopping boundary; a trend was evident toward OS benefit with pertuzumab

Hazard ratio <1 favors pertuzumab

Baselga J et al. *N Engl J Med* 2012b;366(2):109-19.

DR SMITH: The addition of everolimus to exemestane had a major effect on time to recurrence compared to exemestane alone. The hazard ratio was 0.36 by central assessment, suggesting a highly significant delay in time to recurrence (Baselga 2012a; [1.3]).

Before we start administering this combination to every patient, however, we need to consider that the addition of everolimus comes with its own toxicities, including diarrhea, mucositis, hyperglycemia and a small incidence of pneumonitis. I have administered everolimus to some patients and have not encountered any serious problems. It's not as harsh as chemotherapy, but it's not as easy as endocrine therapy. The cost is also a concern.

DR LOVE: Would you also comment on the TAMRAD trial, which evaluated the addition of everolimus to tamoxifen for postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer who had previously received aromatase inhibitors?

DR SMITH: I find it interesting that another study reported a similar benefit. The Phase II TAMRAD trial randomly assigned patients with ER-positive, HER2-negative metastatic breast cancer previously treated with aromatase inhibitors to tamoxifen alone or with everolimus (Bachelot 2010).

The addition of everolimus increased the clinical benefit rate and significantly prolonged the time to progression. Analysis of patients who were resistant to original endocrine therapy and who experienced relapse during adjuvant treatment showed a strong trend for a higher benefit in patients who were resistant to treatment, rather than for those who were still sensitive to it.

Everolimus inhibits the mTOR pathway, which is one mechanism whereby estrogen resistance can be overcome. We need to be able to identify patients who are potentially still sensitive to hormone therapy versus those who are resistant. I believe that we may eventually have a marker to do that. ■

1.3

BOLERO-2 Trial: Exemestane and Everolimus in ER/PR-Positive Metastatic Breast Cancer Refractory to Nonsteroidal Aromatase Inhibitors

Efficacy	Everolimus + exemestane (n = 485)	Placebo + exemestane (n = 239)	HR	*p*-value
Median PFS (by central assessment)	10.6 mo	4.1 mo	0.36	<0.001
ORR (by local assessment)	9.5%	0.4%	—	<0.001
	Everolimus + exemestane (n = 482)		Placebo + exemestane (n = 238)	
Select adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis	56%	8%	11%	1%
Fatigue	33%	<4%	26%	1%
Dyspnea	18%	4%	9%	<2%
Anemia	16%	6%	4%	<2%
Hyperglycemia	13%	<5%	2%	<1%
Pneumonitis	12%	3%	0%	0%

HR = hazard ratio; PFS = progression-free survival; ORR = objective response rate

Baselga J et al. *N Engl J Med* 2012a;366(6):520-9.

SELECT PUBLICATIONS

Bachelot T et al. **TAMRAD: A GINECO randomized Phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast cancer (MBC) with prior exposure to aromatase inhibitors (AI).** San Antonio Breast Cancer Symposium 2010;**Abstract S1-6**.

Baselga J et al. **Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2012a;366(6):520-9.

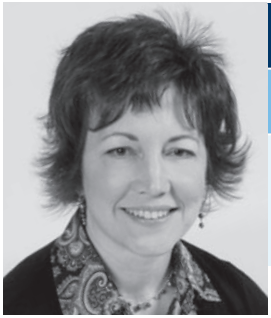
Baselga J et al; CLEOPATRA Study Group. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012b;366(2):109-19.

Constantinidou A, Smith I. **Is there a case for anti-HER2 therapy without chemotherapy in early breast cancer?** *Breast* 2011;20(Suppl 3):158-61.

Gianni L et al. **Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial.** *Lancet Oncol* 2012;13(1):25-32.

Gianni L et al. **Neoadjuvant pertuzumab (P) and trastuzumab (H): Biomarker analyses of a 4-arm randomized Phase II study (NeoSphere) in patients (pts) with HER2-positive breast cancer (BC).** San Antonio Breast Cancer Symposium 2011;**Abstract S5-1**.

Lu D et al. **Drug interaction potential of trastuzumab emtansine combined with pertuzumab in patients with HER2-positive metastatic breast cancer.** *Curr Drug Metab* 2012;[Epub ahead of print].



INTERVIEW

Kathy D Miller, MD

Dr Miller is the Sheila D Ward Scholar of Medicine and Associate Professor of Medicine at The Indiana University Melvin and Bren Simon Cancer Center in Indianapolis, Indiana.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: In which clinical situations have you provided second opinions that commonly differ from those of the first oncologist?

DR MILLER: One issue that comes up frequently is whether or not to administer chemotherapy in the adjuvant setting. We recently had a 43-year-old woman with a Grade I, ER-positive tumor and 1 positive node referred to us for a second opinion by her surgeon, who was surprised that the oncologist had not ordered an Oncotype DX assay.

The patient had basically been told, "You have a positive node and the standard is that you'll receive chemotherapy," and she was literally scheduled for her first treatment the

day after her second-opinion visit with us. One of my partners at Indiana University talked with her about the Onco*type* DX assay, and they agreed it would be helpful in her treatment decision-making process. She ended up having a Recurrence Score of 6. Now she is not getting chemotherapy.

DR LOVE: Have there been other situations in which there has been disparity between your opinion and what the community oncologist recommended?

DR MILLER: I've recently seen 3 patients with metastatic breast cancer whose local oncologist had suggested that they stop trastuzumab because they'd experienced a great response and the oncologist thought it would be a good time for the patients to take a break. I've suggested maybe not.

One patient was a 32-year-old woman with metastatic disease who'd experienced a complete response to chemotherapy/trastuzumab. Chemotherapy had been stopped due to cumulative toxicity, but the patient continued on trastuzumab alone. She was nearing completion of a total year of trastuzumab and it was suggested that she stop. After some discussion the decision was made to continue trastuzumab.

DR LOVE: Would you discuss some of the data that are available to support this approach?

DR MILLER: The strategy of all past trials was to continue trastuzumab at least until progression. We now have data from trials by Drs von Minckwitz (von Minckwitz 2011) and Kim Blackwell (Blackwell 2010) that indicate continuing or reinstituting trastuzumab after progression on trastuzumab-based therapy improves response, progression-free survival and overall survival (2.1). So if continuing or restarting trastuzumab improves overall survival, it seems hard not to come to the conclusion that arbitrarily stopping it would decrease survival.

DR LOVE: Those are certainly interesting cases. In what other areas do these discrepancies arise?

2.1

Continuation of Anti-HER2 Therapy Beyond Disease Progression in Patients with Trastuzumab-Refractory Metastatic Breast Cancer

	GBG 26/BIG 3-05[1,2]		EGF104900[3]	
	Cape	Cape + T	L	L + T
Median TTP[1] or PFS[3]	5.6 mo	8.2 mo	8.1 wk	12.0 wk
	HR, 0.69; $p = 0.0338$		HR, 0.73; $p = 0.008$	
Clinical benefit rate	54.1%	75.3%	12.4%	24.7%
	$p = 0.0068$		$p = 0.01$	
Median overall survival	20.6 mo	24.9 mo	39.0 wk	51.6 wk
	HR, 0.94; $p = 0.73$		HR, 0.75; $p = 0.106$	
Postprogression survival (PPS)*	13.3 mo	18.8 mo	N/E	
	HR, 0.63; $p = 0.02$			

* PPS according to anti-HER2 treatment versus not as part of third-line treatment
Cape = capecitabine; T = trastuzumab; L = lapatinib; TTP = time to progression; PFS = progression-free survival; HR = hazard ratio; N/E = not evaluated

[1] Von Minckwitz G et al. *J Clin Oncol* 2009;27(12):1999-2006; [2] Von Minckwitz G et al. *Eur J Cancer* 2011;47(15):2273-81; [3] Blackwell KL et al. *J Clin Oncol* 2010;28(7):1124-30.

DR MILLER: Issues arise over the use of radiation therapy after breast-conserving surgery in older patients, specifically those older than age 70 for whom we have randomized trial data evaluating the benefits of breast irradiation after lumpectomy in those with ER-positive tumors (Hughes 2010; [2.2]).

I'm often perplexed as to why patients older than age 70 with T1 or T2, ER-positive tumors who've had a lumpectomy rarely hear about the results from that trial. What they hear is, "You had a lumpectomy. You should receive radiation therapy." I've seen women who are 82 and sick who have not heard of this trial even though they tell me they asked the radiation oncologist 3 times, "Do I really need radiation therapy?" because they were worried about toxicity or having to come back and forth because they don't drive or a younger family member has to take off work to bring them.

So these patients come to me for hormone therapy and often ask, "Do I really need this radiation therapy?" There are trade-offs, of course. Radiation oncologists examine these data and say, "Absolutely, radiation therapy works. There was a lower rate of local recurrence."

The issue is the following: Is the difference so great that radiation therapy should be mandated in this setting, or was the risk of local recurrence in women who didn't undergo radiation therapy in a range such that some women would be comfortable saying, "I just don't see the need. At my age, with my other health issues, with all of the logistics and practicalities involved, that just doesn't make sense to me." ■

2.2

CALGB-9343: 10-Year Follow-Up from a Phase III Study of Lumpectomy and Tamoxifen (Tam) with or without Radiation Therapy (RT) for Older Patients (Age 70 or Older) with Early Breast Cancer

	Tam + RT (n = 317)	Tam (n = 319)	*p*-value
Ipsilateral breast tumor recurrence rate	2%	9%	0.0001
10-year overall survival rate	67%	67%	NS
Breast preservation rate	98%	96%	NS
Distant metastasis rate	95%	95%	NS

Conclusions:

- In older women, the benefits of RT after lumpectomy are small.
- With modern margins and use of aromatase inhibitors, RT will likely have even less benefit.
- Omitting RT in women age 70 or older with clinical Stage I breast cancer is a reasonable alternative.

Hughes KS et al. *Proc ASCO* 2010;**Abstract 507**.

SELECT PUBLICATIONS

Blackwell KL et al. **Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer.** *J Clin Oncol* 2010;28(7):1124-30.

Hughes KS et al. **Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer.** *Proc ASCO* 2010;**Abstract 507**.

Von Minckwitz G et al. **Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer.** *Eur J Cancer* 2011;47(15):2273-81.

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

Clifford Hudis, MD

Dr Hudis is Chief of the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-12

Track 1	**Second opinion:** Consideration of forgoing chemotherapy for patients with ER-positive BC with 1 positive node and a low Onco*type* DX Recurrence Score
Track 2	Treatment options for patients with ER-positive, node-negative BC
Track 3	Perspective on efficacy and cardiac safety reported on the BCIRG 006 trial — adjuvant AC → T versus AC → TH or TCH for HER2-positive BC
Track 4	**Second opinion:** A 37-year-old woman with locally advanced, ER-positive, HER2-positive BC treated 3 years ago with neoadjuvant AC → TH followed by tamoxifen who now presents with a 5-mm isolated chest wall nodule
Track 5	Toward incorporating pertuzumab into the treatment algorithm for HER2-positive mBC
Track 6	Mechanisms of action of trastuzumab, trastuzumab-DM1 (T-DM1) and pertuzumab
Track 7	A prospective validation study of the Onco*type* DX DCIS Score™ for predicting recurrence risk after resection alone for DCIS
Track 8	**Second opinion:** A patient with low-risk, ER-negative BC and severe skin toxicity after 2 cycles of adjuvant TC
Track 9	Overview of the BOLERO-2 study: Efficacy, toxicities and proposed adjuvant trials of everolimus in BC
Track 10	Current status of the CALGB-40502 study: Weekly paclitaxel, *nab* paclitaxel or ixabepilone with or without bevacizumab as first-line therapy for locally recurrent or metastatic BC
Track 11	Available research on *nab* paclitaxel
Track 12	Adjuvant bisphosphonate therapy in early BC

Select Excerpts from the Interview

Track 5

DR LOVE: How do you foresee using pertuzumab if it becomes available in the HER2-positive metastatic breast cancer setting?

DR HUDIS: I believe that pertuzumab will quickly be added to standard first-line therapy for HER2-positive metastatic breast cancer. I'm sure we will hear discussion of administering it after progression as second-line therapy and beyond. Although future studies may demonstrate potential activity of pertuzumab in those settings, the big push now is for its use in early breast cancer. The APHINITY trial evaluating adjuvant pertuzumab/trastuzumab is currently accruing patients (3.1).

We have also initiated a nonrandomized Phase II trial of pertuzumab/trastuzumab with weekly paclitaxel in metastatic disease because we recognize that clinicians may prefer weekly paclitaxel as the chemotherapy partner (NCT01276041). We will be reassured

of paclitaxel as a reasonable substitution if the results resemble those from the experimental arm of CLEOPATRA.

3.1

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

Protocol ID: NCT01358877

Target Accrual: 3,806

Eligibility
- HER2-positive primary breast cancer
- ECOG PS ≤1
- Baseline LVEF ≥55%
- No prior anti-HER2 therapy

R

- Chemotherapy + trastuzumab + pertuzumab
- Chemotherapy + trastuzumab + placebo

LVEF = left ventricular ejection fraction

www.clinicaltrials.gov, May 2012.

Track 7

DR LOVE: Would you discuss the SABCS presentation by Dr Solin on the use of the Onco*type* DX assay in DCIS?

DR HUDIS: In this study a subset of the 21 genes from the Onco*type* DX assay were evaluated. Eleven cancer-related genes and 5 reference genes were analyzed and found to be prognostic (Solin 2011; [3.2]). Using the DCIS Score the authors could predict the likelihood of an in-breast event over the coming year.

The problem is that they did not have randomized data for radiation therapy. Although not everyone agrees, it is assumed that the risk is so low, based on the Onco*type* DX DCIS Score being below a certain number, that one could forgo radiation therapy. I believe the role of this test is evolving, and more data are needed. In practice, it would be good if it could be converted from a prognostic to a predictive test, as was done with the Onco*type* DX Recurrence Score.

3.2

ECOG-E5194 Study: 10-Year Outcome of Ipsilateral Breast Events (IBE) by the Onco*type* DX DCIS Score Evaluated by Prespecified Risk Groups

	DCIS Score risk group			
Type of IBE	Low (n = 246)	Intermediate (n = 45)	High (n = 36)	*p*-value*
Any IBE	12.0%	24.5%	27.3%	0.02
Invasive IBE	5.1%	8.9%	19.1%	0.01

* Log-rank *p*-value from a Kaplan-Meier risk curve

"The DCIS Score provides independent information on IBE risk beyond clinical pathologic variables including such important clinical variables as prior tamoxifen use, tumor grade and negative margin width."

Solin LJ et al. San Antonio Breast Cancer Symposium 2011;**Abstract S4-6**.

Tracks 10-11

DR LOVE: Would you talk about the current status of the CALGB-40502 study of first-line chemotherapy for metastatic disease?

DR HUDIS: This is an important trial that compared weekly paclitaxel in the control arm to nanoparticle albumin-bound (*nab*) paclitaxel or ixabepilone in the experimental arms. Most of the patients in this trial received bevacizumab without random assignment because at the time of study design it was anticipated that this would be standard practice. The study had to be halted twice. The first time was due to differential toxicities and the lack of superiority of ixabepilone over weekly paclitaxel for progression-free survival, and the second time was a result of lack of superiority of *nab* paclitaxel versus the control arm. The results will be presented at ASCO.

DR LOVE: Your group recently presented a Phase II trial comparing weekly versus every 2-week or every 3-week *nab* paclitaxel with bevacizumab (Seidman 2011; [3.3]). What are your thoughts about the future of *nab* paclitaxel?

DR HUDIS: It may have promise in the metastatic setting as palliative therapy. In the adjuvant setting, I am not aware of a definitive Phase III trial to establish its role. I believe that in some practices it will be the first choice because of the convenience and lack of premedication. In other practices its use will be restricted because of the cost. ■

3.3

Randomized Phase II Trial of Weekly versus Every 2-Week or Every 3-Week Nanoparticle Albumin-Bound (*Nab*) Paclitaxel with Bevacizumab as First-Line Therapy for Metastatic Breast Cancer

Efficacy	***Nab* paclitaxel q3wk** (n = 75)	***Nab* paclitaxel q2wk** (n = 54)*	***Nab* paclitaxel q1wk** (n = 79)
Overall response	44%	41%	46%
Time to tumor progression (TTP)†	8.0 mo	6.3 mo	9.0 mo
Overall survival (OS)†	21.3 mo	19 mo	23.7 mo
Select adverse events (AEs)			
Sensory neuropathy (Grade ≥2)	64%	67%	70%
Hematologic AEs (Grade ≥3)	18%	8%	30%
Nonhematologic AEs (Grade ≥3)			
Fatigue	17%	35%	18%
Bone pain	3%	6%	1%
Hypertension	4%	2%	4%

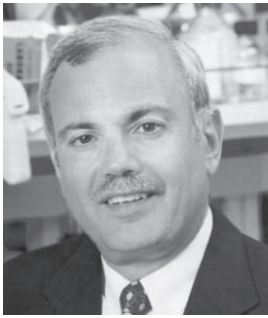
* Every 2-week arm closed early due to significantly more Grade ≥2 fatigue and bone pain
† No statistically significant difference between treatment arms in TTP and OS

Seidman AD et al. San Antonio Breast Cancer Symposium 2011;**Poster P1-14-01**.

SELECT PUBLICATIONS

Baselga J et al. **CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Seidman AD et al. **Randomized Phase II trial of weekly vs q 2-weekly vs q 3-weekly nanoparticle albumin-bound paclitaxel with bevacizumab as first-line therapy for metastatic breast cancer.** San Antonio Breast Cancer Symposium 2011;**Poster P1-14-01**.



INTERVIEW

Dennis J Slamon, MD, PhD

Dr Slamon is Professor of Medicine, Chief of the Division of Hematology/Oncology and Director of Clinical and Translational Research at UCLA's David Geffen School of Medicine in Los Angeles, California.

Tracks 1-16

Track 1 BOLERO-2 results and clinical research on pathways involved in hormone resistance

Track 2 Rationale for the BOLERO-1 trial of everolimus in combination with trastuzumab and paclitaxel in the treatment of HER2-positive locally advanced or metastatic BC

Track 3 Everolimus-associated mucositis and pneumonitis

Track 4 Trials of everolimus/hormonal therapy in the adjuvant setting

Track 5 BCIRG 006 study: Lead investigator's insight on a nonanthracycline regimen (TCH) as an acceptable standard for HER2-positive BC

Track 6 Rationale for investigation of combined blockade of the HER2 and ER pathways

Track 7 Differential response rates to chemotherapy/trastuzumab among patients with ER-positive, HER2-positive versus ER-negative, HER2-positive BC

Track 8 Antibody-drug conjugate strategy in cancer research

Track 9 Results of a Phase II study of T-DM1 versus trastuzumab/docetaxel for previously untreated HER2-positive mBC

Track 10 Perspective on the efficacy and tolerability of trastuzumab/lapatinib in HER2-positive early BC

Track 11 Lessons learned and remaining questions from the Neo-ALTTO and ALTTO studies of dual HER2 blockade

Track 12 Current status of BETH: A Phase III randomized trial of adjuvant chemotherapy/trastuzumab with or without bevacizumab for HER2-positive BC

Track 13 BEATRICE: A Phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for TNBC

Track 14 Duration of anti-angiogenic treatment

Track 15 Investigation of irreversible tyrosine kinase inhibitors — afatinib and neratinib — in BC

Track 16 Perspective on the role of PARP inhibition in BC

Select Excerpts from the Interview

Track 2

DR LOVE: What are your thoughts on the potential role of everolimus in ER-positive and also HER2-positive breast cancer?

DR SLAMON: We have a large preclinical laboratory that is linked to many of our clinical trials and are therefore largely involved with translational studies. Early preclinical studies of everolimus in a panel of breast cancer cell lines revealed that it was most effective in ER-positive and HER2-positive breast cancer. The strategy behind the BOLERO-2 trial of everolimus in ER-positive breast cancer was developed after earlier Phase I trials showed that everolimus was also effective in other cancer types

(Baselga 2012a; [1.3, page 6]). The BOLERO-1 trial is similar in size to BOLERO-2 but studies the use of everolimus in the first line for HER2-positive disease (4.1). Data from the BOLERO-1 trial should be reported soon.

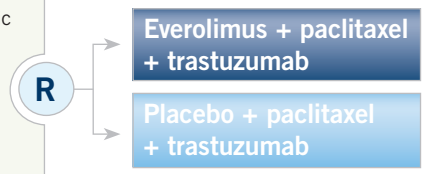
4.1

BOLERO-1: A Randomized Phase III Trial of Everolimus in Combination with Trastuzumab and Paclitaxel as First-Line Therapy for Women with HER2-Positive Locally Advanced or Metastatic Breast Cancer

Protocol ID: NCT00876395 **Target Accrual:** 717

Eligibility

- HER2-positive, locally advanced or metastatic breast cancer with ≥1 measurable lesions or bone metastasis
- Prior endocrine therapy allowed but should be discontinued at randomization
- Prior (neo)adjuvant trastuzumab and/or chemotherapy allowed but discontinued for >1 year prior to randomization



Primary endpoint: Progression-free survival

www.clinicaltrials.gov, May 2012.

Track 5

DR LOVE: Any comments on the BCIRG 006 adjuvant trial in HER2-positive disease now that the results have been formally published?

DR SLAMON: The study went through a number of challenges based on the fact that we were advocating for a nonanthracycline-based regimen in breast cancer treatment, a concept that was not always well received. However, the data from this trial were publicly available long before formal publication and were the basis for the FDA approval of the TCH regimen (Slamon 2011; [4.2]).

Our results indicated a numeric advantage for disease-free survival with the AC → TH over the TCH regimen. The difference between the 2 regimens in the 5-year survival rate was 1%, and the difference in disease-free survival rate was 3%, in favor of the anthracycline-based regimen. These differences were not statistically significant but came at a cost of a statistically significant increase in congestive heart failure and a sustained subclinical loss of cardiac function.

DR LOVE: Would you still feel confident administering TCH to a patient with higher-risk disease — for example, a 50-year-old, otherwise healthy woman with 3 positive nodes?

DR SLAMON: The concept has always been to administer anthracyclines for higher-risk disease. In fact, with larger tumors and those with multiple nodes, even 4 or more, the treatment regimens were identical in terms of the hazard ratios (Slamon 2011). Because no difference was seen in favor of AC → TH, I am comfortable recommending TCH for a patient in this setting.

4.2

BCIRG 006: A Phase III Trial Evaluating AC → T, AC → TH and TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer

Outcome	AC → T (n = 1,073)	AC → TH (n = 1,074)	TCH (n = 1,075)
Estimated 5-year disease-free survival Hazard ratio, *p*-value	75% —	84% 0.64, <0.001	81% 0.75, 0.04
Estimated 5-year overall survival Hazard ratio, *p*-value	87% —	92% 0.63, <0.001	91% 0.77, 0.04
Cardiac-related adverse events	**AC → T**	**AC → TH**	**TCH**
Cardiac-related death	0%	0%	0%
Grade 3 or 4 congestive heart failure	0.7%	2.0%	0.4%*
>10% relative reduction in LVEF	11.2%	18.6%	9.4%†

*$p < 0.001$ for AC → TH versus TCH; †$p < 0.001$ for the comparison between AC → TH and TCH
A = doxorubicin; C = cyclophosphamide; T = docetaxel; H = trastuzumab; LVEF = left ventricular ejection fraction

Slamon D et al. *N Engl J Med* 2011;365(14):1273–83.

Track 9

DR LOVE: What is currently known about the antibody-drug conjugate T-DM1, or trastuzumab maytansine, and in what directions are we headed with this agent?

DR SLAMON: In comparison to the approved trastuzumab/docetaxel regimen in metastatic disease, T-DM1 was numerically superior but not statistically better in terms of response rates. A dramatic improvement in progression-free survival was observed with T-DM1 over the traditional trastuzumab/docetaxel therapy, making T-DM1 a promising agent (Hurvitz 2011; [4.3]). Preclinical studies of T-DM1 and pertuzumab produced favorable results (Honig 2011). Pertuzumab in combination with T-DM1 or trastuzumab is currently being clinically evaluated in the Phase III MARIANNE trial (4.4).

4.3

T-DM1 versus Trastuzumab (T) and Docetaxel (D) for Patients with Untreated HER2-Positive Metastatic Breast Cancer

Efficacy	T + D	T-DM1	Hazard ratio	*p*-value
Objective response rate (n = 69, 67)	58.0%	64.2%	Not reported	
Median PFS (n = 70, 67)	9.2 mo	14.2 mo	0.59	0.035
Median DOR (n = 40, 43)	9.5 mo	Not reached	—	
Select adverse events (AEs)	**T + D** (n = 66)		**T-DM1** (n = 69)	
AE leading to treatment discontinuation*	28.8%		7.2%	
Neutropenia (Grade ≥3)	60.6%		5.8%	
Leukopenia (Grade ≥3)	25.8%		0%	
Thrombocytopenia (Grade ≥3)	3.0%		8.7%	

* Any grade AE
PFS = progression-free survival; DOR = duration of response

Hurvitz S et al. *Proc EMCC* 2011;**Abstract 5001**.

4.4

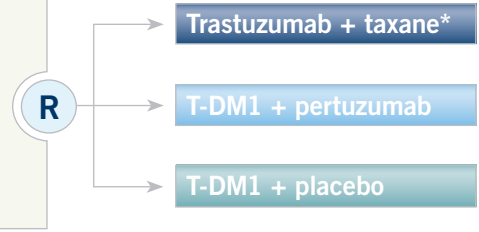
MARIANNE: A Randomized Phase III Trial of T-DM1 in Combination with Pertuzumab versus Trastuzumab in Combination with a Taxane for Patients with Metastatic Breast Cancer

Protocol ID: NCT01120184

Target Accrual: 1,092

Eligibility

- Histologically/cytologically confirmed HER2-positive breast adenocarcinoma
- Locally recurrent or metastatic breast cancer
- Candidate for chemotherapy
- Measurable or nonmeasurable disease per RECIST 1.1



Primary endpoint: Progression-free survival

* Docetaxel or paclitaxel

www.clinicaltrials.gov, May 2012.

Track 15

DR LOVE: What are your thoughts on the investigation of irreversible tyrosine kinase inhibitors (TKIs) in breast cancer?

DR SLAMON: Like lapatinib, neratinib is an active anti-HER2 agent associated with gastrointestinal toxicity (Abbas 2012). This characteristic may limit its use in the adjuvant setting. Afatinib is currently undergoing clinical testing, with the assumption that it has equal or better efficacy than lapatinib without a similar significant toxicity profile. I believe afatinib may have some utility (Lin 2012; [4.5]).

4.5

Phase II Study of Afatinib for Patients with HER2-Positive Metastatic Breast Cancer Progressing After Trastuzumab

Response	All treated patients (n = 41)	Evaluable patients (n = 35)
CR + PR + SD	46%	54%
PR	10%	11%
SD	37%	43%
Progressive disease	39%	46%
Median PFS	15.1 weeks	—
Median overall survival	61.0 weeks	—
Select adverse events (n = 41)	**All grades**	**Grade 3**
Diarrhea	90.2%	24.4%
Rash	65.9%	9.8%

CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival

Lin NU et al. *Breast Cancer Res Treat* 2012;[Epub ahead of print].

4.6

Key Ongoing Phase II/III Trials of Irreversible Tyrosine Kinase Inhibitors for Patients with HER2-Positive Breast Cancer

Trial identifier	Phase	N	Setting	Treatment arms
NCT01125566 (LUX-Breast 1)	III	780	Metastatic	• Trastuzumab/vinorelbine • Afatinib/vinorelbine
NCT00878709 (ExteNET)	III	2,842	Early stage	• Neratinib • Placebo
NCT01441596 (LUX-Breast 3)	II	120	Metastatic	• Afatinib • Afatinib/vinorelbine • Investigator's treatment choice
NCT00706030	I/II	80	Metastatic	• Neratinib/vinorelbine

www.clinicaltrials.gov, May 2012.

Some irreversible TKIs may be better than the reversible agents. That is what the early data indicate with neratinib and afatinib.

The ultimate jury is the clinical trial data, and that jury is still out. These trials are accruing, and the results will determine efficacy (4.6). ■

SELECT PUBLICATIONS

Abbas R et al. **A double-blind, randomized, multiple-dose, parallel-group study to characterize the occurrence of diarrhea following two different dosing regimens of neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor.** *Cancer Chemother Pharmacol* 2012;[Epub ahead of print].

Baselga J et al. **Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2012a;366(6):520-9.

Baselga J et al; CLEOPATRA Study Group. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012b;366(2):109-19.

Honig A et al. **T-DM1 and pertuzumab as new tools for HER2 specific antibody-therapy against breast cancer stem cells in HER2-positive mammary carcinoma.** San Antonio Breast Cancer Symposium 2011;**Abstract P1-04-05**.

Hurvitz S et al. **Trastuzumab emtansine (T-DM1) vs trastuzumab plus docetaxel (H+T) in previously-untreated HER2-positive metastatic breast cancer (MBC): Primary results of a randomized, multicenter, open-label Phase II study (TDM4450g/BO21976).** 2011 European Multidisciplinary Cancer Congress;**Abstract 5001**.

Lin NU et al. **A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab.** *Breast Cancer Res Treat* 2012;[Epub ahead of print].

LoRusso PM et al. **Trastuzumab emtansine: A unique antibody-drug conjugate in development for human epidermal growth factor receptor 2-positive cancer.** *Clin Cancer Res* 2011;17(20):6437-47.

Lu D et al. **Drug interaction potential of trastuzumab emtansine combined with pertuzumab in patients with HER2-positive metastatic breast cancer.** *Curr Drug Metab* 2012;[Epub ahead of print].

Marquette C, Nabell, L. **Chemotherapy-resistant metastatic breast cancer.** *Curr Treat Options Oncol* 2012;[Epub ahead of print].

Perez EZ, Spano JP. **Current and emerging targeted therapies for metastatic breast cancer.** *Cancer* 2011;[Epub ahead of print].

Slamon D et al. **Adjuvant trastuzumab in HER2-positive breast cancer.** *N Engl J Med* 2011;365(14):1273-83.

Villarreal-Garza C et al. **mTOR inhibitors in the management of hormone receptor-positive breast cancer: The latest evidence and future directions.** *Ann Oncol* 2012;[Epub ahead of print].

QUESTIONS (PLEASE CIRCLE ANSWER):

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

2. **The Phase III randomized CLEOPATRA study demonstrated a statistically significant advantage in _____ with the addition of pertuzumab to trastuzumab and docetaxel in patients with metastatic breast cancer.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b
   d. None of the above

3. **Results from the BOLERO-2 Phase III trial of exemestane with or without everolimus for postmenopausal patients with disease refractory to aromatase inhibitors demonstrated significant improvements in response rate and progression-free survival with the addition of everolimus to exemestane.**
   a. True
   b. False

4. **The TAMRAD trial reported no improvement in clinical benefit rate and time to progression with the addition of everolimus to tamoxifen for patients with ER-positive, HER2-negative metastatic breast cancer with prior exposure to aromatase inhibitors.**
   a. True
   b. False

5. **The inclusion of anti-HER2 therapy as part of third-line treatment for patients on the GBG 26/BIG 3-05 trial did not result in a statistically significant improvement in postprogression survival.**
   a. True
   b. False

6. **In a Phase II trial of weekly versus every 2-week or every 3-week *nab* paclitaxel with bevacizumab as first-line therapy for metastatic breast cancer, a statistically significant difference in efficacy was seen among the treatment arms.**
   a. True
   b. False

7. **Prespecified categories of high-, intermediate- and low-risk groups in the ECOG-E5194 study were used in the validation of the Onco*type* DX DCIS Score as a predictor of recurrence of _____.**
   a. Any ipsilateral breast event
   b. Invasive ipsilateral breast events
   c. Both a and b

8. **The Phase III LUX-Breast 1 trial is evaluating trastuzumab/vinorelbine versus _____/vinorelbine for patients with HER2-positive metastatic breast cancer.**
   a. Afatinib
   b. Neratinib
   c. Both a and b

9. **In the Phase III BCIRG 006 trial, the rates of congestive heart failure and cardiac dysfunction were significantly higher in the group of patients receiving AC → TH than in the TCH group.**
   a. True
   b. False

10. **The results of a Phase II trial of T-DM1 versus trastuzumab and docetaxel for patients with untreated HER2-positive metastatic breast cancer demonstrated a significant difference in _____ in favor of T-DM1.**
    a. Objective response rate
    b. Median progression-free survival
    c. Overall survival
    d. Both a and b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 2, 2012

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PART 1 — 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
BOLERO-2 study: Exemestane combined with everolimus in ER/PR-positive metastatic breast cancer refractory to nonsteroidal aromatase inhibitors	4 3 2 1	4 3 2 1
Prospective validation of the Onco*type* DX DCIS Score for predicting recurrence risk after resection alone for DCIS	4 3 2 1	4 3 2 1
CLEOPATRA study: First-line docetaxel/trastuzumab with or without pertuzumab for HER2-positive metastatic breast cancer	4 3 2 1	4 3 2 1
Antitumor effect of adjuvant bisphosphonate therapy in early breast cancer — The NSABP-B-34, ABCSG-12 and AZURE trials	4 3 2 1	4 3 2 1
Investigation of irreversible TKIs — afatinib and neratinib — in breast cancer	4 3 2 1	4 3 2 1
T-DM1 versus trastuzumab/docetaxel in previously untreated HER2-positive metastatic 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
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Use case-based learning to formulate individualized disease-management strategies for patients with breast cancer. . . . . 4 3 2 1 N/M N/A
- Determine the utility of genomic assays in counseling patients with ductal carcinoma in situ or ER-positive early breast cancer about their risk of recurrence and the potential benefits of radiation therapy or adjuvant chemotherapy, respectively . . . . . 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 emerging clinical trial data with novel anti-HER2 agents under investigation in breast cancer.. . . . . 4 3 2 1 N/M N/A
- Recall emerging data on the role of mTOR inhibition in reversing resistance to trastuzumab and endocrine therapy in metastatic breast cancer in preparation for the potential availability of this treatment approach. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic roles of bisphosphonates and other bone-targeted agents in disease management. . . . . 4 3 2 1 N/M N/A

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

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

PART 2 — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Ian E Smith, MD	4 3 2 1	4 3 2 1
Kathy D Miller, MD	4 3 2 1	4 3 2 1
Clifford Hudis, MD	4 3 2 1	4 3 2 1
Dennis J Slamon, 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

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

.....

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