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Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

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INTERVIEW

Edith A Perez, MD

Dr Perez is Deputy Director at the Mayo Clinic Cancer Center, Group Vice Chair of the Alliance of Clinical Trials in Oncology and Serene M and Frances C Durling Professor of Medicine at the Mayo Clinic in Jacksonville, Florida.

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on the results from the recently reported BOLERO-2 trial, which evaluated exemestane and everolimus in patients with ER-positive metastatic breast cancer (mBC) refractory to nonsteroidal aromatase inhibitors?

DR PEREZ: The addition of the mTOR inhibitor everolimus to therapy for patients with mBC refractory to first-line antiestrogen therapy is a significant advance in the treatment of ER-positive disease. The BOLERO-2 trial was well performed. I had the honor of being the chair of the Independent Data Monitoring Committee, so I was able to follow the study from its initiation until the release of the data and its recent publication in *The New England Journal of Medicine* (Baselga 2012; [1.1]). The data from this study are applicable to clinical practice. The addition of everolimus resulted in clear improvements in progression-free survival (PFS) and response rate and showed a trend toward an improvement in overall survival (OS). We need to wait a bit for the results to mature to solidify the survival data.

One of the questions I'm frequently asked is whether I'm going to manage all of my cases of ER-positive disease with this combination. A couple of issues come to mind: First, this study was essentially in the second-line setting, although many patients had received antiestrogens and chemotherapy. But even if everolimus receives approval, I wonder whether that approval will be limited to patients who would have met the BOLERO study criteria. So I do not know if everolimus will be available in the first-line setting. Second, some increased toxicities were evident on the everolimus arm,

1.1

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* 2012;366(6):520-9.

which will be important for clinicians to be aware of and discuss with their patients. The ones I believe to be most relevant are mucositis and some pulmonary toxicity manifested by dyspnea and pulmonary infiltrates.

Track 5

DR LOVE: Would you discuss the SWOG-S0226 trial of first-line anastrozole with or without fulvestrant for postmenopausal women with ER-positive mBC that was presented at the San Antonio meeting (Mehta 2011)?

DR PEREZ: Some of the quirks of this SWOG study are fascinating. A significant number of patients presented with mBC — approximately 40% — which is unusual in the United States, where only approximately 5% of patients first present to a medical oncologist with mBC that has not been pretreated. The data were interesting, but I wonder how applicable they are to the patient population we see here in the United States.

These results were also contradictory to another previously reported trial in this setting that showed no benefit to adding fulvestrant to anastrozole when compared to anastrozole alone in mBC (Bergh 2012; [1.2]). But now that this SWOG study suggests a benefit to adding fulvestrant to anastrozole, I believe we will see a renewed interest in the evaluation of this combination. It will be nice if some follow-up work is performed in this area.

DR LOVE: Another aspect of the SWOG trial is that the investigators used the conventional 250-mg dose of fulvestrant after a loading dose. A number of people have already switched over to the 500-mg dose, so that makes these results a bit more difficult to interpret, correct?

DR PEREZ: Exactly. I believe we need to wait before we start administering fulvestrant and an aromatase inhibitor to patients, considering these conflicting results.

1.2

Anastrozole (A) versus A and Fulvestrant (F) as First-Line Therapy for Postmenopausal Women with ER-Positive Metastatic Breast Cancer

	SWOG-S0226[1]		FACT[2]	
	A (n = 349)	A + F (n = 345)	A (n = 256)	A + F (n = 258)
Median PFS[1] or TTP[2]	13.5 mo	15.0 mo	10.2 mo	10.8 mo
	HR, 0.80; $p = 0.007$		HR, 0.99; $p = 0.91$	
Median OS	41.3 mo	47.7 mo	37.8 mo	38.2 mo
	HR, 0.81; $p = 0.049$		HR, 1.0; $p = 1.0$	
Prior adjuvant endocrine therapy	40.3%	40.4%	65.6%	69.8%

PFS = progression-free survival; TTP = time to progression; HR = hazard ratio; OS = overall survival

[1] Mehta RS et al. San Antonio Breast Cancer Symposium 2011;**Abstract S1-1**; [2] Bergh J et al. *J Clin Oncol* 2012;[Epub ahead of print].

Track 6

DR LOVE: What are your thoughts on the issue of potential antitumor effects with adjuvant bone-targeted therapy for patients with early breast cancer?

DR PEREZ: The more we evaluate this issue, the more convinced I am that a signal is present that we need to follow up on because the totality of the data strongly suggests that bisphosphonates appear to provide a disease-free survival benefit in postmenopausal women or women in a low estrogenic state. The final data analysis recently reported from the NSABP-B-34 study (Paterson 2011) could be added to the data from the ABCSG-12 trial (Gnant 2011) in which premenopausal women received ovarian suppression, and we also have the postmenopausal subset analysis from the AZURE study (Coleman 2011; [1.3]).

I am eager to see data from the D-CARE study (NCT01077154), which includes an adjuvant evaluation of the novel RANK ligand inhibitor denosumab versus placebo to determine whether denosumab can improve disease-free survival. If the D-CARE study is suggestive of a benefit for postmenopausal women, it would be fascinating to then mount a trial comparing zoledronic acid to denosumab for postmenopausal patients with breast cancer.

1.3

Hazard Ratios for Patients with Early Breast Cancer Receiving Adjuvant Bisphosphonates

Disease-free survival	ABCSG-12[1]	AZURE[2]	NSABP-B-34[3]
ITT population	HR, 0.72; $p = 0.014$	HR, 0.98; $p = 0.79$	HR, 0.91; $p = 0.27$
Postmenopausal patients	N/A	HR, 0.75; $p = 0.02$	HR*, 0.76; $p = 0.05$

ITT = intent to treat; HR = hazard ratio
* Secondary endpoint — Relapse-free interval

[1] Gnant M et al. San Antonio Breast Cancer Symposium 2011;**Abstract S1-2**; [2] Coleman RE et al. *N Engl J Med* 2011;365(15):1396-405; [3] Paterson AHG et al. San Antonio Breast Cancer Symposium 2011;**Abstract S2-3**.

Track 9

DR LOVE: Would you provide an update on the TAILORx and RxPONDER trials?

DR PEREZ: TAILORx was the first prospective study to evaluate the Onco*type* DX assay in the setting of ER-positive, node-negative breast cancer. Patients with an intermediate Onco*type* DX Recurrence Score were randomly assigned to antiestrogen therapy alone or antiestrogen therapy and chemotherapy. This study has completed accrual of more than 11,000 patients, and we are awaiting the data.

The RxPONDER trial is a logical follow-up study evaluating patients with 1 to 3 involved axillary lymph nodes, again addressing the same type of question: Do these patients need chemotherapy or can they receive antiestrogens alone (1.4)? More than 250 patients have been enrolled on this study to date. Findings from these studies could be extremely important to patient care.

Tracks 12-13

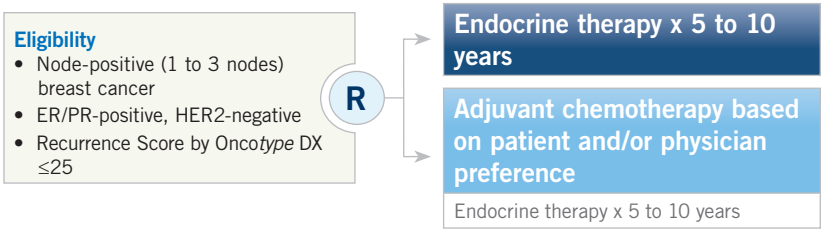
DR LOVE: What is the current status of the CALGB-40502 trial evaluating weekly paclitaxel, nanoparticle albumin-bound (*nab*) paclitaxel or ixabepilone with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer?

1.4

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

Protocol IDs: SWOG-S1007; RxPONDER

Target Accrual: 4,000



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

DR PEREZ: This study evaluated these 3 antitubulin agents administered in a weekly fashion. We now have futility data that indicate that weekly ixabepilone does not appear to be superior to weekly paclitaxel in addition to more recent data that *nab* paclitaxel does not appear to be superior to weekly paclitaxel. So we're going back to square one in terms of the oldest antitubulin agents.

However, one of the critical issues in the CALGB trial is that the dose of *nab* paclitaxel was probably too high. The dose administered was 150 mg/m^2 weekly, whereas plenty of Phase II data suggest that 100 to 125 mg/m^2 of *nab* paclitaxel is efficacious and yields minimal toxicity. I believe that what we observed in this trial was based on the balance of tolerability and efficacy because if we push the dose of *nab* paclitaxel too hard, patients cannot tolerate it.

I anticipate these results will be presented at ASCO this year, and I hope that *nab* paclitaxel evaluation is not discontinued in breast cancer and instead we see a further impetus to evaluate lower doses of this agent to ascertain how it fares against other antitubulin agents.

This agent does have a lower risk of allergic reactions compared to weekly paclitaxel and it allows for diminished use of corticosteroids, which can be important for clinical practice. Additionally, some patients initially develop allergic reactions to paclitaxel, and in those situations *nab* paclitaxel is a reasonable option. I believe there's still a role for *nab* paclitaxel in breast cancer. ■

SELECT PUBLICATIONS

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

Bergh J et al. **FACT: An open-label randomized Phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer.** *J Clin Oncol* 2012;[Epub ahead of print].

Mehta RS et al. **A Phase III randomized trial of anastrozole versus anastrozole and fulvestrant as first-line therapy for postmenopausal women with metastatic breast cancer: SWOG S0226.** San Antonio Breast Cancer Symposium 2011;**Abstract S1-1**.

Paterson AHG et al. **NSABP protocol B-34: A clinical trial comparing adjuvant clodronate vs placebo in early stage breast cancer patients receiving systemic chemotherapy and/or tamoxifen or no therapy — Final analysis.** San Antonio Breast Cancer Symposium 2011;**Abstract S2-3**.

INTERVIEW

Mark D Pegram, MD

Dr Pegram is Director of the Breast Oncology Program, Co-Director of the Experimental Therapeutics Program and Professor of Medicine at Stanford University Medical Center in Stanford, California.

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Track 2 Minimal pertuzumab-related toxicities in the CLEOPATRA study

Track 3 APHINITY: An ongoing Phase III trial evaluating the addition of pertuzumab to chemotherapy/trastuzumab as adjuvant therapy for HER2-positive early-stage BC

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Track 7 Update on status of the irreversible EGFR/HER2 tyrosine kinase inhibitors neratinib and afatinib for HER2-positive mBC

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Track 9 Lessons learned from a Phase III colorectal cancer trial: Revisiting the duration of bevacizumab administration

Track 10 Viewpoint on the initial results with the addition of bevacizumab to trastuzumab/docetaxel in the AVEREL trial

Track 11 Investigation of long-term anti-angiogenic strategies in the treatment of BC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on pertuzumab and the results of the CLEOPATRA study, which was presented at the 2011 San Antonio Breast Cancer Symposium (SABCS)?

DR PEGRAM: Originally, pertuzumab was thought to be effective in diseases without HER2 amplification or overexpression because of its ability to block HER2/HER3 heterodimerization, which is a potent signaling force. It was thought that pertuzumab would have efficacy in HER2-negative diseases such as prostate cancer, non-small cell lung cancer, ovarian cancer and HER2-negative breast cancer. However, in Phase I/II trials this was not the case (Gianni 2010). As such pertuzumab had a "dark horse, latecomer" aspect for many clinical oncologists.

I was pleasantly surprised by the magnitude of the treatment effect of adding pertuzumab to trastuzumab and docetaxel for patients with mBC (Baselga 2012; [2.1]). Pertuzumab extended PFS by 6.1 months. The hazard ratio was 0.62, and the difference was

2.1

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 = 808)	**18.5 months**	**12.4 months**	**0.62**	**<0.001**
(Neo)adjuvant chemotherapy				
With trastuzumab (n = 88)	16.9 months	10.4 months	0.62	NR
No trastuzumab (n = 288)	21.6 months	12.6 months	0.60	NR
Interim OS* (n = 402, 406)	82.8%	76.4%	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* 2012;366(2):109-19.

statistically significant. These impressive results will be practice changing. Because this was a planned interim analysis, the investigators reported few events for the OS analysis. The *p*-value for the OS benefit in the pertuzumab group was 0.005, but it did not meet the O'Brien-Fleming stopping boundary of 0.001. However, it will be interesting to follow up with patients over time because a trend was seen toward a survival benefit. One of the most impressive properties of pertuzumab is that it does not significantly increase toxicity. The study reported a slight increase in neutropenia, mucositis and some low-grade gastrointestinal toxicity, probably because of longer treatment times.

It's important to note that in the CLEOPATRA study few patients received prior adjuvant trastuzumab therapy similar to many of the original pivotal clinical trials of trastuzumab (Eiermann 2001). It is unclear whether the results from these trials can be translated into the modern era and whether pertuzumab will have similar benefits in patients with prior trastuzumab treatment. Clearly, more studies are required with a focus on the patient cohort of the current era who are survivors of adjuvant trastuzumab therapy but with relapsed disease.

Track 8

DR LOVE: Would you discuss the results with the Oncotype DX DCIS genomic analysis score that were presented at SABCS 2011?

DR PEGRAM: I have no doubt that many patients with DCIS are overtreated because, in the historical era, many patients who underwent lumpectomy alone without radiation therapy never experienced relapse. Therefore, Dr Melvin Silverstein hypothesized that a specific group of patients with DCIS could be considered for surgical excision only without radiation therapy (Silverstein 2003). The recent report from the ECOG-E5194 study in a unique nonradiated cohort supports the Silverstein hypothesis. The median age of patients enrolled on the study was 61 years, and all had ER-positive disease (Solin 2011; [2.2]). Most of the patients had low-/intermediate-grade DCIS.

The Onco*type* DX DCIS Score assay evaluated 7 cancer-related and 5 housekeeping genes with most of the genes in the proliferation group and 1 in the steroid group. In the low-risk category, the risk of any ipsilateral breast event was approximately 12% and about 5% for invasive ipsilateral breast events. In the high-risk group, the risk of developing any or invasive ipsilateral breast events was about 27% and 19%, respectively. These results suggested that a study of patients with low-risk DCIS Scores randomly assigned to lumpectomy alone versus lumpectomy with radiation therapy may prove that patients in the low-risk group do not need radiation therapy.

Such a trial is required because it would yield a great clinical effect in a similar manner to the original Onco*type* DX chemotherapy story. Also, the application of the DCIS variant of the Onco*type* DX assay to a modern patient cohort with nonradiation therapy-treated DCIS would be interesting to determine if it holds prognostic significance.

I would consider these to be pilot preliminary data because the ECOG-E5194 parent trial enrolled 670 patients, although tumor samples from only 327 of those patients were subjected to the RT-PCR Onco*type* DX DCIS Score assay. Still these data point strongly toward support of Mel Silverstein's original hypothesis that we're overtreating the vast majority of patients with DCIS.

2.2

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**.

Track 10

DR LOVE: What is your take on the AVEREL trial, which evaluated the addition of bevacizumab to trastuzumab and docetaxel in patients with HER2-positive locally recurrent or metastatic breast cancer?

DR PEGRAM: It is interesting that the AVEREL trial produced a statistically significant PFS with the addition of bevacizumab by independent review assessments conducted in a blinded fashion. However, the investigator assessments reported a *p*-value of 0.07 (Gianni 2011; [2.3]). Overall, the results suggested that the perturbation of VEGF may possess some potential for efficacy, even in HER2-positive mBC.

A PFS advantage of 2.9 months was evident, but no OS effect was observed with the addition of bevacizumab, as assessed by independent review. Although this is a small-scale study, it "opens the door for dusting off bevacizumab" in future investigations in mBC. ■

2.3

AVEREL Trial: Efficacy of Bevacizumab (BEV) in Combination with Trastuzumab (T) and Docetaxel (DOC) as First-Line Therapy for Patients with HER2-Positive Locally Recurrent or Metastatic Breast Cancer

Survival	T + DOC (n = 208)	T + DOC + BEV (n = 216)	Hazard ratio	*p*-value
Median PFS				
INV*	13.7 months	16.5 months	0.82	0.0775
IRC†	13.9 months	16.8 months	0.72	0.0162
Objective response rate	**T + DOC (n = 176)**	**T + DOC + BEV (n = 183)**	**Hazard ratio**	***p*-value**
INV*	69.9%	74.3%	—	0.3492
IRC†	65.9%	76.5%	—	0.0265

PFS = progression-free survival; INV = investigator assessment; IRC = independent review committee assessment
* Unstratified primary analysis per protocol
† Stratified, censored for nonprotocol therapy

Gianni L et al. San Antonio Breast Cancer Symposium 2011;**Abstract S4-8**.

SELECT PUBLICATIONS

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

Eiermann W et al. **Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: Pivotal trial data.** *Ann Oncol* 2001;12(Suppl):57-62.

Gianni L et al. **First results of AVEREL, a randomized phase III trial to evaluate bevacizumab (BEV) in combination with trastuzumab (H) + docetaxel (DOC) as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC).** San Antonio Breast Cancer Symposium 2011;**Abstract S4-8**.

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

Gradishar WJ. **HER2 therapy — An abundance of riches.** *N Engl J Med* 2012;366(2):176-8.

Silverstein MJ. **The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast.** *Am J Surg* 2003;186(4):337-43.

Solin LJ. **Selecting individualized treatment for patients with ductal carcinoma in situ of the breast: The search continues.** *J Clin Oncol* 2012;30(6):577-9.

Solin LJ et al. **A quantitative multigene RT-PCR assay for predicting recurrence risk after surgical excision alone without irradiation for ductal carcinoma in situ (DCIS): A prospective validation study of the DCIS Score from ECOG E5194.** San Antonio Breast Cancer Symposium 2011;**Abstract S4-6**.

INTERVIEW

Beth Overmoyer, MD

Dr Overmoyer is Assistant Professor of Medicine at Harvard Medical School and is affiliated with the Breast Oncology Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-23

Track 1 **Case discussion:** A 52-year-old premenopausal woman with a 7.5-cm, ER/PR-positive, HER2-negative, node-negative interval BC with ductal and lobular features

Track 2 Impact of Onco*type* DX Recurrence Score on selection of adjuvant therapy for ER-positive, node-negative BC

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Track 13 Toward incorporating pertuzumab into the treatment algorithm for HER2-positive mBC

Track 14 Maintaining a patient on single-agent trastuzumab after 5 years of treatment for HER2-positive mBC

Track 15 **Case discussion:** A 30-year-old BRCA1-positive woman with a family history of BC presents with a 6-cm, node-negative TNBC with 8-mm residual disease after neoadjuvant dose-dense AC → dose-dense paclitaxel in combination with bevacizumab followed by mastectomy

Track 16 Activity of bevacizumab for patients with TNBC in the neoadjuvant setting

Track 17 Use of neoadjuvant platinum-containing chemotherapy for TNBC in clinical practice

Track 18 Complete response with a PARP inhibitor in combination with cisplatin for a BRCA1-positive patient with locally recurrent TNBC

Track 19 Use of methadone in the management of chest wall or axillary neuropathic pain

Track 20 Selection of patients with mBC for treatment with *nab* paclitaxel

Track 21 Perspective on the dose schedule and toxicity of *nab* paclitaxel observed in the CALGB-40502 study

Track 22 Objective responses in patients with mBC treated with late-line eribulin

Track 23 **Case discussion:** A 45-year-old woman with a 2.5-cm, Grade II, ER/PR-positive, infiltrating ductal carcinoma with 1 positive node is found to have an Onco*type* DX Recurrence Score of 43 after receiving 3 out of 4 planned cycles of docetaxel/cyclophosphamide

Select Excerpts from the Interview

Tracks 1-5

Case discussion

A 52-year-old premenopausal woman with a 7.5-cm, ER/PR-positive, HER2-negative, node-negative interval BC with ductal and lobular features

DR OVERMOYER: This woman had a mammogram 1 year earlier, with good follow-up, but she subsequently presented to her primary care physician with a palpable mass in her breast. Imaging revealed numerous microcalcifications and a biopsy confirmed invasive ER-positive, HER2-negative invasive carcinoma. She decided to undergo a simple mastectomy. She was also experiencing dysfunctional vaginal bleeding and anticipated undergoing total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO).

I was leaning toward primary hormonal therapy, but I informed her nothing was wrong with receiving chemotherapy in this setting and that with a tumor this large, many physicians would recommend it. I proposed the Onco*type* DX assay to her, and she was very much in favor of it. I understand the assay is not perfect, but it does provide a lot of information that reflects the biology of this disease.

I always discuss with patients beforehand what our objectives will be if they receive an intermediate Recurrence Score — proceed with adjuvant chemotherapy or not. This decision must be made up front. Fortunately, her Recurrence Score was 6, which is low. She subsequently underwent a TAH-BSO and has been receiving an aromatase inhibitor for the past 2 years without any evidence of disease.

DR LOVE: If this patient's tumor were not as large and you were considering neoadjuvant therapy, would you consider ordering an Onco*type* DX assay to help guide the preoperative decision-making process?

DR OVERMOYER: I do order an Onco*type* DX assay in this setting, and if the Recurrence Score is low, I feel comfortable administering primary endocrine therapy, and I inform the patient that it's going to take a longer time to get the adequate response that we want.

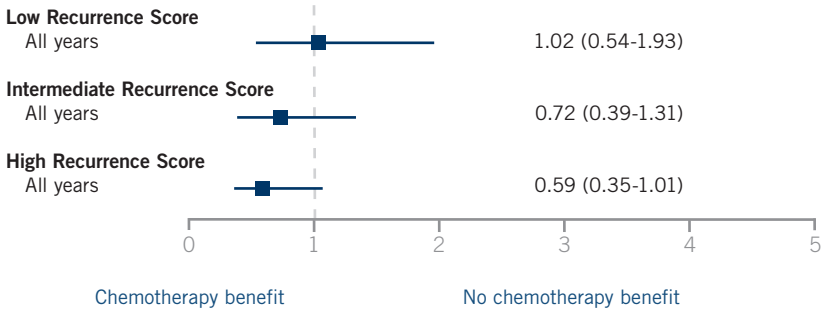
DR LOVE: What is your approach for a patient with node-positive disease, in terms of the role of assays like Onco*type* DX?

DR OVERMOYER: Analysis of data from the SWOG-8814 trial supports a correlation between Onco*type* DX Recurrence Score and outcome in terms of prognosis for postmenopausal patients with node-positive disease (Albain 2010; [3.1]). Unless my patient is highly motivated to go forward with chemotherapy, I discuss the role of the Onco*type* DX assay for patients who have 1 to 3 positive nodes.

I also feel comfortable in pursuing Onco*type* DX analysis to ascertain whether I should administer chemotherapy for patients who are receiving radiation therapy after breast conservation surgery in which a sentinel lymph node dissection has revealed 1 out of 3 involved sentinel lymph nodes without a completion axillary lymph node dissection, following the data from ACOSOG-Z0011.

3.1

Disease-Free Survival Hazard Ratios (95% CI) for Tamoxifen Alone versus CAF → Tamoxifen in Patients with ER-Positive, Node-Positive Breast Cancer According to Oncotype DX Recurrence Score Risk Group



CI = confidence interval

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

Tracks 7-10

Case discussion

A 37-year-old woman with a 4.6-cm, Grade III, ER/PR-negative, HER2-positive, LVI-positive breast cancer with 11 of 14 positive nodes receives adjuvant TAC without trastuzumab in another country in 2007, and her disease recurs with pulmonary metastases 1 year later

DR OVERMOYER: In February 2008 this patient presented with asymptomatic pulmonary metastases and received capecitabine/trastuzumab until disease progression. She was switched to vinorelbine/trastuzumab and tolerated it well for 1 year. I discussed stopping the vinorelbine, which brings up the issue of how long one should continue chemotherapy in patients with metastatic disease. Older data suggest that continuous chemotherapy isn't more effective, but that may not be true with newer agents. I don't know the correct answer, but I was concerned about causing so much bone marrow suppression that I wouldn't be able to administer adequate doses when her disease progressed.

So she continued trastuzumab monotherapy until October 2009 before she experienced minimal disease progression in her lungs. I always like to avoid chemotherapy if possible, and she received lapatinib/trastuzumab until March 2010 before her disease progressed again. At that time, she enrolled on a Phase I study with T-DM1, pertuzumab and paclitaxel and experienced a rapid complete response after 2 cycles. T-DM1 has significantly affected patients who have received a lot of prior HER2-directed therapy, and I look forward to this drug receiving FDA approval. ■

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.

Solin LJ et al. **A quantitative multigene RT-PCR assay for predicting recurrence risk after surgical excision alone without irradiation for ductal carcinoma in situ (DCIS): A prospective validation study of the DCIS score from ECOG E5194.** San Antonio Breast Cancer Symposium 2011;**Abstract S4-6**.

INTERVIEW

Sara A Hurvitz, MD

Dr Hurvitz is Assistant Clinical Professor of Medicine at the University of California, Los Angeles as well as Director of the Breast Oncology Program and Medical Director of the Clinical Research Unit at the Jonsson Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-15

Track 1 **Case discussion:** A 43-year-old woman with ER/PR-negative, HER2-positive mBC who has a complete response to docetaxel/trastuzumab on a clinical trial and crosses over to T-DM1 upon disease progression

Track 2 Results of a Phase II study of T-DM1 versus trastuzumab/docetaxel in previously untreated HER2-positive mBC

Track 3 Adverse events with T-DM1 compared to docetaxel/trastuzumab

Track 4 Mechanism of action of the antibody-drug conjugate T-DM1

Track 5 Relationship of tolerability, duration of treatment and efficacy of T-DM1

Track 6 Applicability of the CLEOPATRA data to patients who received prior adjuvant trastuzumab

Track 7 Redefining the treatment approach to HER2-positive BC in the era of novel agents

Track 8 Targeting the PI3K/AKT/mTOR pathway with everolimus to overcome resistance to trastuzumab and endocrine therapy

Track 9 Results of a Phase I study of everolimus in combination with weekly paclitaxel and trastuzumab for patients with HER2-positive mBC pretreated with trastuzumab

Track 10 BOLERO-1: A Phase III study of everolimus in combination with trastuzumab and paclitaxel as first-line therapy for HER2-positive locally advanced or metastatic BC

Track 11 Everolimus-associated mucositis and pneumonitis

Track 12 Penetration of the blood-brain barrier with everolimus

Track 13 Integrating everolimus into the treatment of endocrine-resistant mBC

Track 14 Progression-free survival as an endpoint in clinical trials

Track 15 Perspective on the current status of bevacizumab in BC

Select Excerpts from the Interview

Tracks 2-5

DR LOVE: Would you discuss your Phase II study comparing T-DM1 to trastuzumab/docetaxel as first-line therapy for patients with mBC?

DR HURVITZ: On this study 137 patients with HER2-positive, untreated mBC were randomly assigned to trastuzumab/docetaxel or T-DM1. Notably, only 27% of patients on the control arm received trastuzumab in the adjuvant setting compared to 18% on the study arm. PFS, the primary endpoint in the study, was 14.2 months with T-DM1 — 5 months more than with trastuzumab/docetaxel. This was associated with a 41% relative risk reduction for PFS, which was statistically significant. The objective

response rates and clinical benefit rates were similar between the 2 groups (Hurvitz 2011; [4.1]).

Of note, the median duration of docetaxel treatment on the control arm was 5.5 months versus 10 months with T-DM1 alone. This suggests that the tolerability of trastuzumab/docetaxel is different than T-DM1. Patients were able to receive T-DM1 much longer than the full trastuzumab/docetaxel combination because of the targeted delivery of T-DM1 to cancer cells.

Also of profound importance on this study was the difference in adverse events (AEs) between the 2 arms (4.1). Grade 3 or higher AEs were observed in 89% of the patients on the trastuzumab/docetaxel arm compared to only 46% on the T-DM1 arm. That is a huge difference. Serious AEs were also higher for patients on the control arm. Rates of AEs leading to treatment discontinuation were 7% with T-DM1 versus 29% with trastuzumab/docetaxel. The vast majority of patients — approximately 96% — on the T-DM1 arm did not lose their hair, which is an important clinical endpoint from a patient's perspective. Overall, T-DM1 was a much better tolerated therapy.

The most common side effects of T-DM1 are fatigue and nausea. Some patients experience an elevation in their AST or ALT. The all-grade thrombocytopenia was higher with T-DM1, and the incidence of Grade 3/4 thrombocytopenia was approximately 9% on the T-DM1 arm and 3% on the trastuzumab/docetaxel arm.

DR LOVE: In your opinion, what is the reason for the improved efficacy of T-DM1?

DR HURVITZ: I believe the duration of treatment is an important reason why T-DM1 yields more efficacy because the response rates between the 2 treatment arms are similar.

4.1

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

Efficacy	Trastuzumab + docetaxel	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	NR*	Not reported	

Select adverse events (AE)	Trastuzumab + docetaxel (n = 66)	T-DM1 (n = 69)
Any Grade ≥3 AE	89.4%	46.4%
AE leading to treatment discontinuation (any grade)	28.8%	7.2%
Serious AE (any grade)	25.8%	18.8%
Neutropenia (Grade ≥3)	60.6%	5.8%
Leukopenia (Grade ≥3)	25.8%	0%
Thrombocytopenia (Grade ≥3)	3.0%	8.7%
Alopecia (Grade 1-2)	66.7%	4.3%

PFS = progression-free survival; DOR = duration of response
* NR = not reached; longer follow-up needed to estimate DOR for the T-DM1 arm

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

T-DM1 is trastuzumab that is linked to a derivative of maytansine, which is an incredibly cytotoxic chemotherapy. The "magic" in T-DM1 is that the thioether linker does not release the maytansine until it is inside the tumor cell. So the other possibility is that we're able to deliver highly potent chemotherapy to cancer cells. EMILIA, a Phase III study comparing T-DM1 to capecitabine and lapatinib, completed enrollment at the end of 2011. The results from this study should be available this year and will help us determine the true efficacy of this agent (NCT00829166).

Tracks 8, 13

DR LOVE: Would you discuss the use of the mTOR inhibitor everolimus to overcome resistance to trastuzumab and endocrine therapy?

DR HURVITZ: Everolimus, also known as RAD-001, is an mTOR complex I inhibitor. HER2 activates the PI3-kinase/AKT/mTOR pathway, which is known to be involved in trastuzumab-resistant disease (Nagata 2004). A number of groups have reported data preclinically and through neoadjuvant studies that this appears to be a mechanism of resistance to both trastuzumab and endocrine therapy (Ghayad 2010). It appears that a close interaction exists between the mTOR and ER pathways. Preclinical models suggest that targeting mTOR may overcome trastuzumab resistance in HER2-positive disease and endocrine resistance in ER-positive disease (LoPiccolo 2008). Data from our laboratory indicated that approximately 60% of the HER2-positive cell lines and more than two thirds of the ER-positive or luminal subtypes demonstrated sensitivity to everolimus. These data and similar results from other groups provided support to clinically explore everolimus in these 2 subsets of breast cancer.

DR LOVE: If everolimus is approved for breast cancer, how do you foresee using it in your practice?

DR HURVITZ: I would not administer everolimus in the up-front setting because we do not have data to support its use there. I would administer it for endocrine-resistant disease. Beyond that, will I always administer everolimus in combination with exemestane? Will I use it with tamoxifen, as was done in the TAMRAD study (Bachelot 2010), or with fulvestrant for select patients? I have to say I probably will. If a patient has experienced disease progression on exemestane in the past, then I'm going to pair everolimus with a different agent because the data are interesting and exciting and there's no reason to think that it wouldn't work with another one of these agents. ■

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**.

Ghayad SE et al. **Endocrine resistance associated with activated ErbB system in breast cancer cells is reversed by inhibiting MAPK or PI3K/Akt signaling pathways.** *Int J Cancer* 2010;126(2):545-62.

Hurvitz S et al. **Trastuzumab emtansine (T-DM1) versus 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).** *Proc EMCC* 2011;**Abstract 5001**.

LoPiccolo J et al. **Targeting the PI3K/Akt/mTOR pathway: Effective combinations and clinical considerations.** *Drug Resist Update* 2008;11(1-2):32-50.

Nagata Y et al. **PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients.** *Cancer Cell* 2004;6(2):117-27.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Results from the BOLERO-2 Phase III trial of exemestane with or without everolimus for postmenopausal patients with disease progression on letrozole or anastrozole demonstrated significant improvements in response rate and PFS with the addition of everolimus to exemestane.**
   a. True
   b. False

2. **Which of the following toxicities were associated with the addition of everolimus to exemestane for patients with ER/PR-positive mBC refractory to nonsteroidal aromatase inhibitors in the BOLERO-2 trial?**
   a. Stomatitis
   b. Fatigue
   c. Dyspnea
   d. Anemia
   e. All of the above

3. **The Phase III SWOG-S0226 trial of anastrozole versus anastrozole and fulvestrant as first-line therapy for postmenopausal women with mBC reported statistically significant improvements in _____ for patients receiving anastrozole and fulvestrant.**
   a. Median PFS
   b. Median OS
   c. Both a and b

4. **The Phase III AZURE study, which randomly assigned patients to receive standard adjuvant systemic therapy with or without zoledronic acid, reported an improvement in disease-free survival in which of the following patient populations receiving zoledronic acid?**
   a. Intent-to-treat patient population
   b. Postmenopausal patients
   c. Both a and b

5. **The Phase III randomized CLEOPATRA study demonstrated a statistically significant advantage in _____ with the addition of pertuzumab to trastuzumab and docetaxel in patients with mBC.**
   a. OS
   b. PFS
   c. Both a and b
   d. None of the above

6. **In the validation study of the ECOG-E5194 trial, the Onco*type* DX DCIS Score for the identification of patients with DCIS who do not need radiation therapy after surgical excision was significantly predictive of recurrence of _____ when evaluated by prespecified categories: high-, intermediate- and low-risk groups.**
   a. Any ipsilateral breast event
   b. Invasive ipsilateral breast events
   c. Both a and b

7. **In the randomized Phase III AVEREL trial, the addition of bevacizumab to trastuzumab and docetaxel as first-line therapy demonstrated statistically significant improvements in PFS and OS in patients with HER2-positive locally recurrent or metastatic breast cancer when the investigators performed an unstratified analysis.**
   a. True
   b. False

8. **A retrospective analysis of prospective randomized trial SWOG-8814 suggested that postmenopausal patients with ER-positive, node-positive disease and _____ Onco*type* DX Recurrence Scores experienced significant benefit from the addition of adjuvant CAF chemotherapy to tamoxifen.**
   a. High
   b. Low
   c. Intermediate
   d. All of the above

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

10. **A Phase II study comparing T-DM1 to trastuzumab/docetaxel as first-line therapy for patients with HER2-positive mBC reported a PFS of 9.2 months with trastuzumab/docetaxel versus 14.2 months with T-DM1.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 1, 2012

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 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: Exemestane combined with everolimus in ER/PR-positive mBC refractory to nonsteroidal aromatase inhibitors	4 3 2 1	4 3 2 1
SWOG-S0226: First-line anastrozole with or without fulvestrant for postmenopausal women with ER-positive mBC	4 3 2 1	4 3 2 1
Antitumor effect of adjuvant bone-targeted therapy in early breast cancer — NSABP-B-34, ABCSG-12, AZURE and D-CARE	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: First-line docetaxel/trastuzumab with or without pertuzumab for HER2-positive mBC	4 3 2 1	4 3 2 1
AVEREL: Bevacizumab in combination with first-line trastuzumab/docetaxel for HER2-positive locally recurrent or metastatic breast cancer	4 3 2 1	4 3 2 1
T-DM1 versus trastuzumab/docetaxel in previously untreated HER2-positive mBC	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 1 or more examples:

.....

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

☐ Yes ☐ No

If no, please explain: .....

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

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

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

- Determine the utility of genomic assays in counseling patients with DCIS 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 patients diagnosed with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings. . . . . 4 3 2 1 N/M N/A
- Evaluate the unique mechanisms of action and emerging clinical trial data with novel anti-HER2 agents under investigation in breast cancer.. . . . . 4 3 2 1 N/M N/A
- Formulate individualized approaches to first- and later-line therapy for patients with HER2-negative metastatic 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 role 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
Edith A Perez, MD	4 3 2 1	4 3 2 1
Mark D Pegram, MD	4 3 2 1	4 3 2 1
Beth Overmoyer, MD	4 3 2 1	4 3 2 1
Sara A Hurvitz, 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:

.....

.....

.....

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