INTERVIEW

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Tracks 1-20

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Track 2 Toxicities associated with everolimus in the BOLERO-2 study

Track 3 Evaluation of everolimus in earlier BC disease settings

Track 4 Rationale for ongoing BOLERO-1 and BOLERO-3 Phase III studies of everolimus in combination with chemotherapy/trastuzumab in HER2-positive locally advanced or metastatic BC

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Track 11 Continued debate on defining a role for bevacizumab in the treatment of BC

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Track 15 Tolerability of adjuvant lapatinib

Track 16 Superiority of first-line trastuzumab-DM1 (T-DM1) versus docetaxel/trastuzumab in a Phase II study

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Track 20 Addition of bevacizumab to first-line docetaxel/trastuzumab for HER2-positive mBC in the Phase III AVEREL study

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

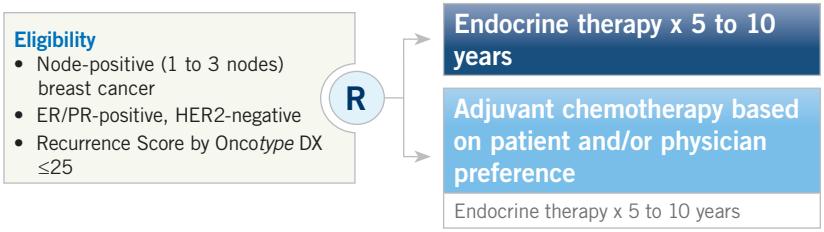
DR LOVE: What is the current status of the CALGB-40502 trial evaluating weekly paclitaxel, nanoparticle albumin-bound (*nab*) paclitaxel or ixabepilone with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer?

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**.