INTERVIEW

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the Phase III CALGB-40502 study you presented at ASCO, evaluating 3 microtubule inhibitors as first-line therapy for metastatic breast cancer?

DR RUGO: The goal of the trial was to determine whether *nab* paclitaxel and ixabepilone would be superior to paclitaxel in terms of PFS or equivalent and have less toxicity. For the study, 799 women with chemotherapy-naïve, metastatic, HER2-normal breast cancer were randomly assigned to weekly paclitaxel, *nab* paclitaxel

or ixabepilone (Rugo 2012; [2.1]). Bevacizumab was administered to almost all the patients. After the recommendation that bevacizumab approval for mBC be withdrawn, bevacizumab use was made optional. However, 98% of patients received bevacizumab.

Hematologic toxicity was greater for *nab* paclitaxel compared to paclitaxel. Peripheral and motor neuropathy was higher for both experimental arms. The ixabepilone arm was closed early due to futility. Eventually the entire study was halted for the same reason. The results showed that both the ixabepilone and *nab* paclitaxel arms had a shorter PFS compared to paclitaxel. These newer agents offered the promise of being able to reverse resistance in this patient population, but paclitaxel was as good or better.

DR LOVE: Outside a research setting, do you utilize *nab* paclitaxel and at what dose?

DR RUGO: Yes, definitely. I believe *nab* paclitaxel has an important place in the treatment of advanced breast cancer in patients who cannot tolerate the solvent Cremophor® or steroids. For patients with preexisting peripheral neuropathy, I administer *nab* paclitaxel at a lower dose of 100 mg/m^2 as a measure to avoid the additional toxicity of Cremophor. I have never administered the higher dose of 150 mg/m^2 used in the trial and I would not now.

2.1

CALGB-40502 Study: Weekly Paclitaxel versus *Nab* Paclitaxel or Ixabepilone with or without Bevacizumab for Locally Recurrent or Metastatic Breast Cancer

Efficacy	***Nab* paclitaxel** (n = 271)	**Paclitaxel** (n = 283)	**Ixabepilone** (n = 245)
Median progression-free survival	9.2 mo	10.6 mo	7.6 mo
	Nab paclitaxel vs paclitaxel HR = 1.19, $p = 0.12$ Ixabepilone vs paclitaxel HR = 1.53, $p < 0.0001$		
Select Grade ≥3 adverse events	***Nab* paclitaxel** (n = 258)	**Paclitaxel** (n = 262)	**Ixabepilone** (n = 237)
Hematologic	51%	21%	12%
Nonhematologic	60%	44%	56%
Motor neuropathy	10%	2%	6%
Sensory neuropathy	25%	16%	25%

Rugo HS et al. *Proc ASCO* 2012;**Abstract CRA1002**.

Track 3

DR LOVE: At San Antonio last year for the first time we saw data on an Onco*type* DX assay in DCIS (Solin 2011; [2.2]). What were your thoughts about that?

DR RUGO: The Onco*type* DX Recurrence Score® was the first test that was able to predict who might benefit the most from adjuvant chemotherapy. That is a critical question for patients with ER-positive early-stage breast cancer. Hopefully, over time and with more data, we'll be able to make similar decisions for patients with DCIS.

With the Onco*type* DX DCIS assay, we're not deciding if a patient should receive chemotherapy or not. We're trying to identify patients with low-risk DCIS who can undergo surgery only, without the need for radiation therapy. Slow-growing DCIS could be managed with a fairly conservative approach in elderly patients. The Onco*type*

DX DCIS Score will help us understand who needs less therapy as opposed to us utilizing the same approach for everyone.

2.2

ECOG-E5194 Study: 10-Year Outcome of Ipsilateral Breast Events (IBE) by the Oncotype 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 6-7

DR LOVE: Would you discuss the BOLERO-2 trial, which evaluated exemestane and everolimus for patients with ER-positive locally advanced or metastatic breast cancer refractory to nonsteroidal aromatase inhibitors (AIs)?

DR RUGO: The results of BOLERO-2 are exciting because it is the first trial that showed that hormone resistance could be reversed (Baselga 2012; [2.3]). We worked hard to find tissue biomarkers that would determine who might respond to the addition of everolimus to standard hormone therapy. We never found a biomarker, but

2.3

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 or 4	All grades	Grade 3 or 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.

we found that if you administer a steroidal AI such as exemestane to patients who have experienced disease progression on an AI, you have already selected a group of patients in whom this pathway may be activated.

The addition of everolimus to exemestane resulted in a longer PFS. Fewer deaths occurred on that arm, but the OS endpoint has not yet been reached. It is intriguing that everolimus appears to be associated with some bone effects, with preservation of bone density as opposed to the bone loss that we see with AIs.

We would like to prevent relapse and death in patients who have developed resistance rapidly or have up-front resistance to hormone therapy. A trial adding everolimus for patients with higher-risk, ER-positive, early-stage breast cancer is planned. Moving forward it will be critical to find the subgroup of patients who will benefit from everolimus.

Oncologists need to be aware of the toxicity profile of this agent and to dose reduce everolimus and hold the drug when patients develop mouth sores and, rarely, interstitial pneumonitis.

DR LOVE: How significant is the pneumonitis when everolimus is combined with hormonal therapy, and how do you screen patients for it?

DR RUGO: Pneumonitis is not as much of an issue as we feared it might be. It occurs in less than 1% of patients and is usually mild. Patients who develop a cough or interstitial changes on a CT scan and are asymptomatic must be watched carefully. The agent should be held, if necessary, and if the dose is reduced many patients can go back on the drug without a problem.

DR LOVE: What are your thoughts on the BOLERO-1 and BOLERO-3 Phase III studies of everolimus in combination with chemotherapy/trastuzumab in HER2-positive locally advanced or metastatic breast cancer?

DR RUGO: These trials are investigating the addition of everolimus to trastuzumab for first-line and later-line therapy. Data from a Phase II trial reported that the addition of everolimus to trastuzumab for patients with progressive disease on trastuzumab-based therapy resulted in clinical benefit and disease response in a reasonable number of patients (Morrow 2011). So we know that mTOR inhibitors have some ability to counter resistance to trastuzumab in HER2-positive breast cancer. These small molecules also cross the blood-brain barrier and may fill a unique niche for treating metastatic, resistant, HER2-positive 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.

Hurvitz SA et al. **BOLERO-1: A randomized, phase III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and paclitaxel as first-line therapy in women with HER2-positive (HER2+), locally advanced or metastatic breast cancer (BC).** *Proc ASCO* 2012;**Abstract TPS648**.

Morrow PK et al. **Phase I/II study of trastuzumab in combination with everolimus (RAD001) in patients with HER2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy.** *J Clin Oncol* 2011;29(23):3126-32.

Rugo HS et al. **CALGB 40502/NCCTG N063H: Randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC).** *Proc ASCO* 2012;**Abstract CRA1002**.