INTERVIEW

Ruth O'Regan, MD

Dr O'Regan is Professor and Vice-Chair for Educational Affairs in the Georgia Cancer Center for Excellence Department of Hematology and Medical Oncology at Grady Memorial Hospital and is the Louisa and Rand Glenn Family Chair in Breast Cancer Research at Winship Cancer Institute of Emory University in Atlanta, Georgia.

Tracks 1-9

Track 1 Background for the development of the BOLERO-3 trial: Trastuzumab/vinorelbine with or without everolimus for HER2-positive locally advanced or metastatic BC

Track 2 Potential incorporation of everolimus into the treatment algorithm for HER2-positive mBC

Track 3 Side-effect management and dose titration with everolimus

Track 4 **Second opinion:** A 59-year-old woman with Stage IV, ER/PR-negative, HER2-positive BC previously treated with TCH followed by 4 years of single-agent trastuzumab presents with liver metastases

Track 5 Selection of patients with mBC for treatment with *nab* paclitaxel

Track 6 Results from a Phase II trial evaluating use of the Onco*type* DX assay RS to select neoadjuvant therapy for ER-positive BC

Track 7 Prognostic impact of the Onco*type* DX RS in patients with Stage IV BC

Track 8 Use of the Onco*type* DX assay for patients with BC and locoregional recurrence

Track 9 Perspective on the utility of the Onco*type* DX assay in node-positive BC

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you provide a brief background on the rationale for studying everolimus in HER2-positive breast cancer? Also, would you comment on the results from the Phase III BOLERO-3 trial of everolimus in combination with trastuzumab/vinorelbine in trastuzumab-resistant HER2-positive metastatic breast cancer that you presented at ASCO 2013?

DR O'REGAN: Preclinical data in trastuzumab-resistant breast cancer models have shown an activation of the PI3 kinase pathway. This occurs either through increased signaling through other growth factor receptors rather than HER2, such as HER3 or insulin growth factor receptor 1, or it can occur constitutively or through PTEN loss. We've performed early-phase trials evaluating mTOR inhibition as a means of enhancing the activity of trastuzumab and maybe reversing resistance to trastuzumab.

One such trial evaluated the combination of paclitaxel/trastuzumab administered weekly with everolimus in patients with heavily pretreated trastuzumab-resistant disease. All patients also had prior taxane exposure, and we reported a high clinical benefit rate of more than 70% (Andre 2010).

Several Phase III BOLERO trials are now ongoing in the HER2-positive setting. BOLERO-1 is evaluating the addition of everolimus to paclitaxel/trastuzumab in the first-line setting, and BOLERO-3 is evaluating the proof of principle that inhibiting mTOR with everolimus may improve outcomes for patients with trastuzumab-resistant breast cancer.

Patients on the BOLERO-3 trial were randomly assigned to weekly vinorelbine and trastuzumab with or without everolimus, and the mTOR inhibitor was administered at 5 mg daily because that was the maximum tolerated dose taken forward from the Phase IB trial. BOLERO-3 met its primary endpoint in that the addition of everolimus to trastuzumab/vinorelbine significantly improved progression-free survival by 1.2 months with a hazard ratio of 0.78 (O'Regan 2013; [3.1]).

Numerically the advantage was not that great, but the survival data are not yet mature, though a trend toward a survival advantage is evident. That analysis will be important because these are patients with heavily pretreated disease.

DR LOVE: Do you believe buried in these modest results might be a population of patients who can derive substantial benefit?

DR O'REGAN: The subgroup analysis performed on this study was interesting, so I say absolutely. We are also performing correlative analyses on samples from approximately 40% of patients on the study, including evaluating different parts of the PI3 kinase pathway, mutations of the PI3 kinase pathway, PTEN, et cetera. The results will be reported at ESMO, and we've seen an indication that some subgroups benefit. From the data that we have so far, the most striking thing in my mind was the fact that the benefit was fairly significant in ER/PR-negative cancer, but no difference was observed in the ER-positive/PR-positive group.

3.1

BOLERO-3: A Phase III Trial of Weekly Trastuzumab and Vinorelbine in Combination with Everolimus or Placebo for Trastuzumab-Resistant, HER2-Positive Metastatic Breast Cancer

Efficacy	Everolimus arm (n = 284)	Placebo arm (n = 285)	Hazard ratio	*p*-value
Median progression-free survival	7.0 mo	5.78 mo	0.78	0.0067
Deaths*	36.3%	41.1%	—	—
Overall response rate	40.8%	37.2%	—	—
Clinical benefit rate	59.2%	53.3%	—	0.09
	Everolimus arm (n = 280)		**Placebo arm** (n = 282)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Stomatitis	63%	13%	28%	1%
Pyrexia	39%	3%	23%	1%
Rash	25%	0%	18%	1%
Hyperglycemia	9%	6%	5%	3%
Hyperlipidemia	2%	0%	1%	0%

* Statistical significance not yet reached at interim overall survival analysis

O'Regan R et al. *Proc ASCO* 2013;**Abstract 505**.

DR LOVE: What's the typical side-effect profile for this agent, and how do you advise patients before starting therapy?

DR O'REGAN: I typically outline the more common side effects — mouth sores, rashes, nail changes. You have to be proactive with the mouth sores. Using "magic mouthwash" with steroids appears to be helpful. Also, metabolic abnormalities — hyperglycemia and hyperlipidemia — are some of the tricky aspects. It's difficult to say how we should manage those in general, but I've seen a few patients with diabetes who experienced more elevated blood glucose while receiving everolimus.

Trying to ascertain the right dose for each patient is also an issue. I start with 10 mg for every patient, but I end up reducing the dose to 5 mg or even 2.5 mg a day for patients who can't tolerate the agent. Body mass index appears to play a role in how patients tolerate the drug. Some of my patients with low body mass indexes have experienced more problems. We're working on a pharmacokinetic study to see if we can gain more insight as to what the correct dose is for each patient.

I believe it's important to start with 10 mg in the ER-positive setting because that's what was used in the BOLERO-2 trial, and then you can dose reduce if need be. Some patients may need 10 mg, and you're missing that window by starting at 5 mg.

DR LOVE: In what situations in the metastatic HER2-positive disease setting do you envision using everolimus?

DR O'REGAN: Based on the BOLERO-3 data and if it were approved in this setting, I would lean toward administering it in patients with ER/PR–negative cancer who have gone through the other treatments, including pertuzumab and T-DM1 and perhaps lapatinib. That might be a group for whom you're starting to run out of options.

Tracks 6, 9

DR LOVE: Would you discuss the results of your Phase II study evaluating the use of the Onco*type* DX assay RS to select neoadjuvant therapy for patients with ER-positive breast cancer?

DR O'REGAN: Obviously, the TAILORx study is ongoing and will provide the "gold standard" with regard to use of the Onco*type* DX assay in the adjuvant setting once it is completed. But our Phase II study was initiated a number of years ago because quite often oncologists must administer preoperative treatment.

Similar to the design of the TAILORx trial, we were attempting to use RS to help us select therapies, except this was in the neoadjuvant setting. Patients with an RS of 25 or higher received docetaxel/cyclophosphamide (TC). Those with an RS of 10 or less received neoadjuvant endocrine therapy, and those in the intermediate group were randomly assigned to endocrine therapy or TC.

The number of evaluable patients is somewhat small, but we observed a pathologic complete response rate of approximately 20% in patients with high RS who received TC. Of note, in the intermediate RS group we did not observe any pathologic complete responses among the patients who received TC, although it is clear that chemotherapy can downstage these tumors because radiologically we observed decreases in tumor size (Zelnak 2013; [3.2]).

3.2

Results from a Phase II Trial Evaluating the Use of the Onco*type* DX Assay Recurrence Score (RS) to Select Neoadjuvant Therapy for ER-Positive Breast Cancer

	RS ≤ 10	11 ≥ RS < 25		RS ≥ 25
Clinical response	**Exemestane** (n = 9)	**Exemestane** (n = 9)	**TC x 6** (n = 10)	**TC x 6** (n = 18)
Complete response	33.3%	22.2%	40%	44.4%
Partial response	44.4%	66.7%	50%	44.4%
Radiologic response				
Complete response	0%	0%	40%	11.1%
Partial response	66.7%	66.7%	50%	55.6%
Pathologic CR	0%	0%	0%	22.2%
BCS	28.6%	50%	40%	61.1%

TC = docetaxel/cyclophosphamide; CR = complete response; BCS = breast-conserving surgery

- Results from the Phase III TAILORx and RxPONDER trials will provide additional information regarding use of adjuvant chemotherapy in patients with intermediate RS.
- For patients with ER-positive breast cancer who are referred for preoperative therapy prior to BCS, incorporation of the Onco*type* DX assay RS should be considered.

Zelnak AB et al. *Proc ASCO* 2013;**Abstract 562**.

One of the issues we struggle with in administering preoperative endocrine therapy is not administering it long enough. So we designed this trial so patients received preoperative endocrine therapy for at least 6 months, and we tried to keep them on it until they achieved maximum response. We performed ultrasounds every 2 months on the study. I would say that it's unclear how long you need to administer endocrine therapy in this setting. Of course, another issue was that pathologic complete response is not that important in these ER-positive tumors, particularly luminal A ER-positive disease.

DR LOVE: How do you use the Onco*type* DX assay in the adjuvant setting?

DR O'REGAN: We use the 21-gene RS in virtually all cases of node-negative breast cancer, unless the tumors are tiny. I've actually run into a couple of patients recently for whom one of the surgeons has ordered the assay for a 6-mm tumor and the RS is 24, and I was thinking, "What am I going to do with that information?"

I also order it frequently for patients with 1 to 3 positive lymph nodes, although my preference is to place such patients on the SWOG-S1007 study (RxPONDER). Because our surgeons are proactive about ordering the 21-gene RS, I've been reminding them to send patients over to us first, so we can get them on the study. ■

SELECT PUBLICATIONS

Andre F et al. **Phase I study of everolimus plus weekly paclitaxel and trastuzumab in patients with metastatic breast cancer pretreated with trastuzumab.** *J Clin Oncol* 2010;28(34):5110-5.

Jerusalem G et al. **Phase I trial of oral mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine in pre-treated patients with HER2-overexpressing metastatic breast cancer.** *Breast Cancer Res Treat* 2011;125(2):447-55.

O'Regan R et al. **Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3).** *Proc ASCO* 2013;**Abstract 505**.

Zelnak AB et al. **Phase II trial evaluating the use of 21-gene Recurrence Score (RS) to select preoperative therapy in hormone receptor (HR)-positive breast cancer.** *Proc ASCO* 2013;**Abstract 562**.