INTERVIEW

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Tracks 1-9

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Track 2 Management of everolimus-associated mucositis

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Track 5 Interim safety results of a Phase II trial of eribulin and ramucirumab for mBC

Track 6 Accessing bevacizumab for patients with mBC via participation in early-phase clinical trials

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Track 9 Selection of patients with mBC for treatment with *nab* paclitaxel

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your treatment algorithm for patients with ER-positive, HER2-negative metastatic breast cancer?

DR YARDLEY: This is a group of patients who were not embraced initially in many clinical trials or in the development of our understanding of the pathways in metastatic breast cancer. But now as molecular biologists have begun to unravel data with regard to endocrine resistance mediated by the estrogen receptor, we've witnessed the development of the BOLERO-2 trial evaluating the addition of everolimus to the aromatase inhibitor (AI) exemestane. And that approach is now an approved strategy for patients with metastatic breast cancer that has progressed on an AI (Baselga 2012; [3.1]).

I perform biopsies for these patients, not so much to establish disease recurrence but to develop a molecular profile. This initiative provides a wealth of information about the tumor. The probability is high for patients with metastatic ER-positive disease that they harbor PI3K mutations, and we prefer to place such patients on clinical trials if possible. For patients who are not trial candidates or who do not wish to enroll on trials, my preference is to administer everolimus and an AI. I don't typically administer the combination of an AI with fulvestrant.

DR LOVE: What are your experiences with managing everolimus-associated mucositis?

DR YARDLEY: We do not have a "one size fits all" answer because it seems that some patients are susceptible to this side effect and others "sail through" therapy. My approach is this: I meet with patients soon after everolimus therapy begins. The nurses and I inform patients that we want to know about the development of toxicities early on. If needed, I institute rapid dose reductions or even dose delays, let the patient recover and then perhaps drop the dose from 10 mg to 5 mg and work it back up. This is a valuable treatment if you can get the patient over the initial hurdles of some of the toxicities that are so different from those of hormonal therapy alone.

DR LOVE: What is the typical clinical evolution of this mucositis, and how does it compare to chemotherapy-related mucositis?

DR YARDLEY: Mucositis associated with chemotherapy is much more broad and encompassing of the entire mucosa of the oral cavity and can occur throughout the entire gastrointestinal tract. Everolimus-associated mucositis is distinct. The ulcers are discontinuous and have a shallower base, making them more amenable to topical approaches.

Patients can experience mucositis within the first 2 weeks to 28 days of beginning everolimus. Educating patients is key because we want them to realize that we do not have to discontinue this effective agent. We need their help to manage the side effect early on with a dose delay of everolimus while they continue to receive the AI and let the lesions heal. Then we can reinitiate everolimus therapy perhaps with a dose reduction.

3.1

BOLERO-2: A Phase III Trial of 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 and central 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.

Tracks 3-5

DR LOVE: What are your thoughts on the results of the Phase III study comparing eribulin to capecitabine for locally advanced or metastatic breast cancer?

DR YARDLEY: This trial was performed in a much earlier clinical setting than that which led to the approval of eribulin. So it was designed to move eribulin up earlier in the metastatic setting and to ascertain whether it was superior to capecitabine. The trial population had a lot of heterogeneity. Patients with HER2-positive breast cancer were allowed on the trial, and as we now start going back and trying to ascertain where the signals were if that subgroup was removed, it is interesting that eribulin appears to have been more effective in patients with HER2-negative disease in addition to those with triple-negative breast cancer (Kaufman 2012; [3.2]).

So even though the trial didn't meet its primary objective, I believe it has a number of interesting facets that we're now trying to channel toward an understanding of a potential molecular target in certain patient subgroups.

DR LOVE: How do you integrate eribulin into your practice outside of a trial setting, and how do you sequence it in relation to capecitabine?

DR YARDLEY: Our practice has openly embraced eribulin since its approval, and I believe in trying to use it in several ways. I sequence it much earlier in my algorithm for patients with metastatic HER2-positive disease. Data on the combination of eribulin and trastuzumab for locally recurrent or metastatic HER2-positive breast cancer were presented by Dr Linda Vahdat at the 2012 San Antonio Breast Cancer Symposium (Vahdat 2012). I have administered this regimen, and it's a well-tolerated combination.

I also integrate eribulin much earlier for patients with HER2-normal disease. I've administered it as second-line therapy. We are awaiting data from a trial of eribulin with ramucirumab as second- or third-line therapy for metastatic breast cancer.

3.2

Phase III Study of Eribulin versus Capecitabine for Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

Median OS	Eribulin	Capecitabine	Hazard ratio	*p*-value
Overall (n = 554, 548)	15.9 mo	14.5 mo	0.879	0.056
HER2 status				
HER2-positive	14.3 mo	17.1 mo	0.965	NR
HER2-negative	15.9 mo	13.5 mo	0.838	NR
ER status				
ER-positive	18.2 mo	16.8 mo	0.897	NR
ER-negative	14.4 mo	10.5 mo	0.779	NR
Triple-negative				
Yes	14.4 mo	9.4 mo	0.702	NR
No	17.5 mo	16.6 mo	0.927	NR
Select adverse events	**Eribulin** (n = 544)		**Capecitabine** (n = 546)	
Grade	All	3 or 4	All	3 or 4
Neutropenia	54%	46%	16%	<5%
Leukopenia	31%	15%	10%	<3%

OS = overall survival; NR = not reported

Kaufman PA et al. San Antonio Breast Cancer Symposium 2012;**Abstract S6-6**.

Eribulin is also being evaluated in patients who have residual disease after neoadjuvant anthracycline- or taxane-based therapy (3.3).

DR LOVE: Ramucirumab is an novel anti-angiogenic agent with known activity in gastric cancer. Unlike bevacizumab, which binds the ligand, it binds the VEGF receptor. What do we know about this agent in breast cancer?

DR YARDLEY: I believe a particular group of patients clearly benefited from bevacizumab, so when we were approached with a potential trial including ramucirumab in the metastatic setting we were eager to embrace it. Ramucirumab seems to have a little less toxicity in terms of hypertension and some of the other cumbersome toxicities of bevacizumab. We've recently presented the interim safety results from a Phase II study of ramucirumab and eribulin for patients with metastatic disease. Ramucirumab combined well with eribulin, and we did not observe any added features of toxicity (Yardley 2012). ■

3.3

Key Ongoing Phase II Trials Evaluating Eribulin-Based Therapy for Patients with Breast Cancer

Trial identifier	N	Setting	Treatment arms
NCT01427933	141	• Metastatic • HER2-positive	• Eribulin + ramucirumab • Eribulin
E-VITA/GBG 64 (NCT01534455)	80	• Metastatic • HER2-positive	• Eribulin (1.23 mg) + lapatinib • Eribulin (1.76 mg) + lapatinib
NCT01593020	152	• Neoadjuvant • HER2-negative	• Eribulin → FAC or FEC • Paclitaxel → FAC or FEC
NCT01388647	56	• Neoadjuvant • HER2-positive	• Eribulin + trastuzumab + carboplatin
NSABP-FB-9 (NCT01705691)	50	• Neoadjuvant • HER2-negative	• Eribulin → AC • Paclitaxel → AC
NCT01439282	67	• Adjuvant • ER-positive, HER2-negative	• Eribulin + capecitabine

F = 5-FU; A = doxorubicin; C = cyclophosphamide; E = epirubicin

www.clinicaltrials.gov, July 2013.

SELECT PUBLICATIONS

Campone M et al. **Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: Subgroup analysis from the BOLERO-2 study.** *Eur J Cancer* 2013;49(12):2621-32.

Kaufman PA et al. **A Phase III, open-label, randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.** San Antonio Breast Cancer Symposium 2012;**Abstract S6-6**.

Vahdat L et al. **Eribulin mesylate + trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer: Results from a Phase 2, multicenter, single-arm study.** San Antonio Breast Cancer Symposium 2012;**Abstract P5-20-04**.

Yardley DA et al. **Interim safety results of eribulin (E) combined with ramucirumab (RAM) in patients (pts) with advanced metastatic breast cancer (MBC).** Breast Cancer Symposium 2012;**Abstract 110**.