INTERVIEW

Joyce O'Shaughnessy, MD

Dr O'Shaughnessy is Co-Director of the Breast Cancer Research Program at Baylor-Charles A Sammons Cancer Center in Dallas, Texas.

Tracks 1-16

Track 1 Biologic rationale for the study of iniparib in triple-negative BC (TNBC)

Track 2 Results of Phase II and III clinical trials of iniparib with chemotherapy for metastatic TNBC

Track 3 Iniparib-associated DNA damage via inhibition of the telomere pathway

Track 4 Exploration of the effectiveness of chemotherapy/iniparib for patient subtypes with metastatic TNBC

Track 5 **Case 1 discussion:** A 27-year-old woman with a 1-cm x 1.5-cm Grade I, ER/PR-positive, HER2-negative, node-negative BC with an Onco*type* DX® Recurrence Score® (RS) of 24

Track 6 Evaluation of the benefits of adjuvant chemotherapy for patients with an intermediate RS in the TAILORx study

Track 7 Impact of a high RS in node-negative versus node-positive BC

Track 8 **Case 2 discussion:** A woman in her early sixties with locally advanced, ER/PR-positive, HER2-negative BC with bone and liver metastases

Track 9 Weekly paclitaxel/capecitabine for rapidly progressive, ER-positive metastatic BC (mBC)

Track 10 Use of reduced-dose eribulin for patients with mBC and elevated bilirubin

Track 11 Clinical experience with eribulin in various subtypes of mBC

Track 12 **Case 3 discussion:** A 36-year-old woman with locally advanced ER/PR-negative, HER2-positive, Grade III infiltrating ductal carcinoma and biopsy-proven liver metastases

Track 13 Trastuzumab, lapatinib and reduced-dose capecitabine for progressive mBC

Track 14 Capecitabine with or without trastuzumab for patients with HER2-positive mBC and disease progression on trastuzumab

Track 15 Activity of capecitabine in ER-negative versus ER-positive mBC

Track 16 Toward a new era of identifying and targeting genetic aberrations in ER-positive BC

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you discuss the biologic rationale for your study of iniparib for patients with triple-negative breast cancer (TNBC)?

DR O'SHAUGHNESSY: This trial was based on the concept of synthetic lethality, which means that a tumor cell in which BRCA1 or BRCA2 doesn't work properly is reliant on PARP for its DNA repair. So if you hit the cell with DNA-damaging chemotherapy and then also inhibit PARP, the cell dies because it has no way to repair its DNA.

We performed a Phase II trial of the PARP inhibitor iniparib in patients with TNBC (O'Shaughnessy 2011b) because data exist showing that some cases of TNBC are like BRCA1-related tumors, which have a substantial defect in their ability to repair double-strand breaks.

We didn't have a way to select for patients with problems with homologous recombination, the double-strand DNA repair mechanism, so we included "all comers" with TNBC in the randomized Phase II trial.

We chose gemcitabine/carboplatin (GC) because they are both DNA-damaging agents leading to single-strand breaks, which are converted to double-strand breaks in rapidly proliferative cancer such as TNBC. Among 123 patients with TNBC we observed a large improvement in overall and progression-free survival, response rates and clinical benefit rates even though 51% of patients who received GC alone crossed over to GC and iniparib at the time of disease progression (O'Shaughnessy 2011b).

For the Phase III trial we entered the same patient population. We enrolled 519 patients with rapid recruitment, with many patients who'd received adjuvant doxorubicin with cyclophosphamide followed by a taxane entering our trial immediately after disease recurrence. We had a higher rate of cross-over on the Phase III trial — 96% of patients on the GC arm who experienced disease progression crossed over to GC and iniparib.

Much to our disappointment, we did not see a statistically significant improvement in the coprimary endpoints of progression-free and overall survival (O'Shaughnessy 2011a; [2.1]). If we'd had one or the other as a primary endpoint, the study would have been positive.

We did report a signal in the second- and third-line patient population. The data looked good (2.1), but perhaps it's not large enough in a mixed population of patients to make it significant. It is possible that what's buried in that signal is a subpopulation of patients who benefit from this combination. Everyone agrees that's what we must find out.

An enormous amount of work is now ongoing to evaluate the patient populations between the Phase II and Phase III trials. We saw tremendous variability among patient subtypes in the Phase III trial.

TNBC is heterogeneous. Thus the hope is that we will be able to identify a subtype of TNBC in which GC and iniparib provide a benefit. By the end of the year, we plan to have an answer to that question. An important finding that's come to light is that although iniparib inhibits PARP as a protein, the physiologically achievable concentrations of iniparib we administer in humans are not inhibiting PARP.

2.1

Phase III Trial of Gemcitabine/Carboplatin (GC) with or without Iniparib (I) for Metastatic Triple-Negative Breast Cancer

	GC (n = 258)	GCI (n = 261)	Hazard ratio	*p*-value
Intent-to-treat (ITT) population				
Median OS	11.1 mo	11.8 mo	0.88	0.280
Median PFS	4.1 mo	5.1 mo	0.79	0.027
Exploratory analysis: Second-/third-line ITT population				
	GC (n = 109)	GCI (n = 113)	Hazard ratio	*p*-value
Median OS	91 mo	108 mo	0.65	0.012
Median PFS	29 mo	43 mo	0.67	0.011

OS = overall survival; PFS = progression-free survival

O'Shaughnessy J et al. *Proc ASCO* 2011a;**Abstract 1007**.

An interesting report from Dr Ji and colleagues analyzed olaparib, veliparib and iniparib in a TNBC cell line. They reported evidence of DNA-damaged double-strand breaks with all 3 agents. However, when they performed gene expression profiling on the cell lines to ascertain what was being inhibited, they found that olaparib and veliparib inhibited PARP1 and PARP2 but iniparib did not.

What they found was that iniparib was interfering with maintenance of telomeres, which are the ends of the chromosomes that need to be maintained by a whole host of enzymes for the chromosomes to be able to continue to divide (Ji 2011).

Telomeres are extremely important to these rapidly growing cells, and when you inhibit the telomere pathway, you get a crushing amount of DNA damage and the cell has a necrotic-like death.

Tracks 10-11

DR LOVE: What are your thoughts on the use of eribulin for patients with metastatic breast cancer (mBC)?

DR O'SHAUGHNESSY: Eribulin is an interesting new agent that was approved by the FDA late last year. We have to exercise caution in the setting of elevated liver function, but if you refer to the package label insert for eribulin, you'll see that for up to a Child-Pugh A category you're allowed to administer eribulin at a lower dose (2.2).

With the taxanes, ixabepilone and vinorelbine, we don't go near a patient with elevated bilirubin. I find the eribulin package insert and safety experience with lower doses helpful.

I have recently administered eribulin to a patient in this setting. Her disease had progressed through a number of treatments and she had come in with elevated bilirubin, significant ascites and lower-extremity edema. I administered reduced-dose eribulin, and her liver function tests improved. She diuresed about 45 pounds, had no ascites and the bilirubin normalized.

I'm also extremely impressed with the non-cross resistance of eribulin with the other agents we use in patients with metastatic disease. I'm trying to understand where else I can administer eribulin now.

For my own practice experience, I'd like to know more about the more classical triple-negative type that's not a BRCA1 germline mutation. In the EMBRACE trial, if you evaluate the forest plot with regard to overall survival, the point estimate is clearly in favor of eribulin, and it's as favorable in the triple-negative population (Cortes 2011b). ■

2.2

Dose and Administration of Eribulin Mesylate for Patients with Metastatic Breast Cancer and Impaired Liver Function

Recommended dose — administered IV over 2 to 5 minutes on days 1 and 8 of a 21-day cycle

Patients with **normal** hepatic function	Patients with **mild** hepatic impairment (Child-Pugh A)	Patients with **moderate** hepatic impairment (Child-Pugh B)
1.4 mg/m^2	1.1 mg/m^2	0.7 mg/m^2

Eribulin mesylate [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2010. Available at: **http://us.eisai.com/pdf_files/Halaven_PI.pdf**.

SELECT PUBLICATIONS

Cortes J, Vidal M. **Beyond taxanes: The next generation of microtubule-targeting agents.** *Breast Cancer Res Treat* 2011a;[Epub ahead of print].

Cortes J et al. **Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study.** *Lancet* 2011b;377(9769):914-23.

Eribulin mesylate [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2010. Available at: **http://us.eisai.com/pdf_files/Halaven_PI.pdf**.

Fojo T et al. **Potential pitfalls of crossover and thoughts on iniparib in triple-negative breast cancer.** *J Natl Cancer Inst* 2011;[Epub ahead of print].

Gelmon KA et al. **Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study.** *Lancet Oncol* 2011;12(9):852-61.

Ji J et al. **Pharmacodynamic and pathway analysis of three presumed inhibitors of poly (ADP-ribose) polymerase: ABT-888, AZD2281, and BSI201.** *Proc AACR* 2011;**Abstract 4527**.

Lin NU, Burstein HJ. **EMBRACE, eribulin, and new realities of advanced breast cancer.** *Lancet* 2011;377(9769):878-80.

O'Shaughnessy J et al. **A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ASCO* 2011a;**Abstract 1007**.

O'Shaughnessy J et al. **Iniparib plus chemotherapy in metastatic triple-negative breast cancer.** *N Engl J Med* 2011b;364(3):205-14.