INTERVIEW

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Tracks 1-21

Track 1 **Case discussion:** A woman in her midforties develops bone and liver metastases three years after receiving dose-dense AC → paclitaxel for node-positive, triple-negative BC (TNBC)

Track 2 Activity of platinum agents in TNBC

Track 3 Use of chemotherapy/bevacizumab in metastatic TNBC (mTNBC)

Track 4 Second- and later-line treatment of mTNBC

Track 5 Mechanism of action of antitubulins

Track 6 Bevacizumab-associated nasal side effects

Track 7 Carboplatin/gemcitabine and iniparib in mTNBC

Track 8 Survival as an endpoint of clinical trials of first-line therapy for mBC

Track 9 Perspective on the EMBRACE study results with eribulin in patients with heavily pretreated mBC

Track 10 **Case discussion:** A 71-year-old woman presents with an ER-positive, HER2-positive, node-positive locally advanced BC and concomitant pulmonary metastases

Track 11 Orally administered pan-HER TKI neratinib under investigation in HER2-positive mBC

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Track 13 Endocrine therapy in combination with trastuzumab in ER-positive, HER2-positive mBC

Track 14 Activity of neoadjuvant pertuzumab/trastuzumab in the NEOSPHERE trial

Track 15 Trastuzumab/lapatinib in HER2-positive mBC

Track 16 T-DM1: Direct delivery of maytansinoid to cancer cells abrogates chemotherapy-related toxicity

Track 17 Chronic anti-HER2 therapy for patients with HER2-positive mBC

Track 18 **Case discussion:** A 57-year-old woman with a 1.6-cm, moderately differentiated, ER-positive, HER2-negative, node-negative BC with an Onco*type* DX® Recurrence Score® of 17

Track 19 Development of an Onco*type* DX prostate cancer (PC) test to be used in conjunction with Gleason Score and other PC clinical parameters

Track 20 Use of the Onco*type* DX assay in patients with node-positive BC

Track 21 Investigation of genomic assays in the neoadjuvant setting

Select Excerpts from the Interview

Tracks 3, 6

DR LOVE: The use of chemotherapy and bevacizumab is a bit murky for metastatic breast cancer in light of the current FDA and ODAC stance. What is your current nonprotocol approach to using bevacizumab?

DR BURSTEIN: I still use paclitaxel and bevacizumab in the metastatic setting, based on the strength of the ECOG-E2100 data (Miller 2007). I was not convinced by the AVADO, RIBBON 1 or RIBBON 2 trial data that adding bevacizumab materially improves outcomes in terms of time to disease progression, response or symptom control with other agents (Brufsky 2009; Miles 2010; Robert 2011). I believe, assuming the ECOG-E2100 data remain robust, a substantial difference still exists compared to the other chemotherapies.

However, bevacizumab is not without its side effects, including headaches, high blood pressure and nasal congestion — we typically see postnasal drip, chronic sinus congestion, semipurulent discharge and blood-tinged nasal secretions. I don't have a precise definition and I can't say that the incidence is well described in the literature, but in my experience it's prevalent.

For refractory triple-negative tumors I am inclined to offer bevacizumab because of the sense that chemotherapy alone isn't enough. Triple-negative tumors have a faster rate of progression, so the shift in progression-free survival is narrower in absolute terms.

Track 7

DR LOVE: Would you discuss the updated data with iniparib in TNBC?

DR BURSTEIN: PARP enzymes are involved in DNA repair, and iniparib was initially developed for TNBC because triple-negative tumors have so-called "BRCAness," which is to say they are particularly genetically unstable.

The original presentation at ASCO 2009 reported an improvement in response rate, time to disease progression and overall survival with iniparib and gemcitabine/carboplatin (O'Shaughnessy 2011a). In the Phase III study, eligibility was similar — metastatic TNBC, with many cases being refractory to treatment — and the randomization was also gemcitabine/carboplatin with or without iniparib. However, the results of the study did not meet the coprimary endpoints of improvement in overall survival and progression-free survival (O'Shaughnessy 2011b; [2.1]).

Track 12

DR LOVE: What are your thoughts on some of the new agents being investigated for HER2-positive breast cancer?

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 (95% CI)	*p*-value
Intent-to-treat (ITT) population				
Median OS	11.1 mo	11.8 mo	0.88	0.284
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 (95% CI)	*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* 2011b;**Abstract 1007**.

DR BURSTEIN: It's a great time for new agent development in HER2-positive breast cancer because once you know a target, it's easy to go after it. We have trastuzumab, which is the antibody that targets HER2, and we have next-generation antibody products. Pertuzumab targets both HER2 and HER3, and T-DM1, a conjugated trastuzumab molecule, targets HER2. Lapatinib is a dual kinase inhibitor of EGFR and HER2. Neratinib and afatinib are competing in the sense that they are also dual kinase inhibitors that are orally available and may have a similar niche in treating patients who have failed prior anti-HER2 therapy (2.2).

2.2

Ongoing Trials of Anti-HER2 Therapy for Patients with HER2-Positive Metastatic Breast Cancer Previously Treated with Trastuzumab

Trial identifier	Phase	N	Treatment arms
NCT01125566	III	780	Afatinib/vinorelbine Trastuzumab/vinorelbine
NCT00829166	III	980	T-DM1 Capecitabine/lapatinib
NCT00777101	II	233	Neratinib Capecitabine/lapatinib
NCT01026142	II	450	Capecitabine/trastuzumab/pertuzumab Capecitabine/trastuzumab

www.clinicaltrials.gov, July 2011.

Track 16

DR LOVE: What are your thoughts on T-DM1, the trastuzumab-chemotherapy conjugate?

DR BURSTEIN: T-DM1 is an exciting agent. Robust responses occur in patients who've received prior trastuzumab- and lapatinib-based therapy. The response rate is approximately 30 percent (Burris 2011; [2.3]), and it's now in definitive Phase III trials. T-DM1 is composed of trastuzumab conjugated to a maytansinoid chemotherapy agent called DM1. In the past, by the time investigators reached sufficient cytotoxic doses of DM1 to kill the tumor, the patient was often moribund.

What the researchers have done now is to chemically link DM1 to trastuzumab, creating T-DM1. Each molecule of trastuzumab has three or four molecules of DM1, which enables a more targeted delivery of the chemotherapy directly to the cancerous cell while avoiding the severe toxicities seen in the past.

2.3

Phase II Study of T-DM1 for the Treatment of HER2-Positive Metastatic Breast Cancer After Prior HER2-Directed Therapy

	T-DM1 (n = 112)	
	Independent review facility	Investigator assessment
Objective response rate	25.9%	37.5%
Median progression-free survival	4.6 months	4.6 months
Median duration of response	Not reached	9.4 months

Burris HA et al. *J Clin Oncol* 2011;29(4):398-405.

Track 20

DR LOVE: Would you discuss the current trial of Oncotype DX in node-positive disease?

DR BURSTEIN: The RxPONDER trial is a re-creation of the TAILORx study with node-positive disease instead of node-negative disease (2.4). The stakes are higher in node-positive disease. My threshold for offering chemotherapy is different. If I know I will be administering chemotherapy or if the patient is younger or premenopausal and has multiple positive nodes, then I don't order the assay. We don't have data for premenopausal patients with node-positive disease. In those cases, I don't lean too hard on the test.

However, it has become increasingly clear in recent years that a small amount of nodal disease is not a bad prognostic factor. In NSABP studies, nodal metastases up to two millimeters were not prognostically significant if patients received adjuvant therapy. For those patients, the biological principles of Oncotype DX are likely relevant and a low Recurrence Score probably means that the benefit from chemotherapy is negligible.

DR LOVE: You have commented that the issue is not about prognosis but about whether a benefit is obtained from treatment. Theoretically, some patients with 10 positive nodes may have chemotherapy-unresponsive tumors.

2.4

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

Eligibility
- Node-positive (1 to 3 nodes) breast cancer
- ER/PR-positive, HER2-negative
- Recurrence Score by Oncotype DX ≤25

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Endocrine therapy x 5 to 10 years

Adjuvant chemotherapy based on patient and/or physician preference

Endocrine therapy x 5 to 10 years

www.clinicaltrials.gov. Identifier NCT01272037, June 2011.

DR BURSTEIN: I don't mind administering chemotherapy to a patient with 10 positive nodes because that patient has high-risk cancer and it is reasonable to do everything possible to help the patient.

On the other end of the spectrum, a patient with a 1.5-mm focus of cancer in the lymph node probably has a prognosis similar to a patient with node-negative disease, and it's much more reasonable to consider the value of adjuvant chemotherapy. I reiterate that the important issue is not about prognosis. Patients need to know whether or not a treatment will change their risk of recurrence. ■

SELECT PUBLICATIONS

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Hickish T et al. **Use of BIBW 2992, a novel irreversible EGFR/HER2 tyrosine kinase inhibitor (TKI), to treat patients with HER2-positive metastatic breast cancer after failure of treatment with trastuzumab.** *Proc ASCO* 2009;**Abstract 1023**.

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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* 2011b;**Abstract 1007**.

Robert NJ et al. **RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer.** *J Clin Oncol* 2011;29(10):1252-60.