INTERVIEW

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Tracks 1-14

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Track 2 Ongoing clinical trials evaluating novel agents for patients with HER2-positive BC and brain metastasis

Track 3 Management of brain metastasis with stereotactic radiosurgery alone

Track 4 HALT MBC: A Phase III study of HER2 suppression with the addition of lapatinib to trastuzumab in HER2-positive mBC

Track 5 Efficacy results from a Phase II study of the irreversible ErbB family blocker afatinib (BIBW 2992) for patients with HER2-positive mBC progressing after trastuzumab

Track 6 Toxicities associated with the irreversible EGFR/HER2 TKIs afatinib and neratinib for HER2-positive mBC

Track 7 Critical appraisal of anthracycline- and nonanthracycline-containing adjuvant regimens in HER2-positive BC

Track 8 **Case discussion:** A 60-year-old woman with a Grade III, ER/PR-positive, HER2-negative IDC with 5 of 6 residual positive lymph nodes is randomly assigned to adjuvant bevacizumab/metronomic chemotherapy and dietary intervention on the ABCDE trial

Track 9 Efficacy of metronomic chemotherapy in combination with bevacizumab in advanced BC

Track 10 Challenges for inclusion and evaluation of lifestyle interventions in clinical trials

Track 11 Influences of metformin and lifestyle-directed interventions on patient outcomes

Track 12 **Case discussion:** A 45-year-old premenopausal woman with a Grade I, ER/PR-positive, HER2-negative IDC, a negative sentinel lymph node biopsy and an Onco*type* DX assay Recurrence Score of 17

Track 13 Perspective on the utility of the Onco*type* DX assay in node-positive and large node-negative BC

Track 14 RxPONDER: A Phase III trial of adjuvant endocrine therapy with or without chemotherapy for patients with node-positive BC and a Recurrence Score of 25 or lower

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What's new in terms of management of patients with breast cancer and brain metastases?

DR LIN: No systemic agents have been approved for the indication of brain metastasis. However, a number of trials are ongoing in this setting, and some of them are promising. One Phase II trial with multiple study sites across the country is evaluating GRN1005 in both breast cancer and non-small cell lung cancer. This agent was active in a Phase I trial for patients with advanced solid tumors (Kurzrock 2012).

Another study being opened nationally within the Translational Breast Cancer Research Consortium is evaluating the HER2-targeted agent neratinib, which is an oral tyrosine kinase inhibitor (TKI) similar to lapatinib. In a Phase II trial in the non-CNS setting, the response rates were around 25% in patients with trastuzumab-refractory breast cancer.

Some data were also presented recently from the LANDSCAPE trial, which evaluated the combination of lapatinib and capecitabine. In contrast to the way many clinical trials for patients with brain metastases are conducted, the investigators evaluated this combination as initial therapy at the time of brain metastasis presentation. As a result, these patients generally had less heavily pretreated disease than do most patients we tend to enroll on brain metastasis trials.

The authors reported a high response rate in the brain — more than 60% (Bachelot 2011; [4.1]). In terms of safety, they did not observe many patients with symptomatic disease progression while on trial. The patients who did experience disease progression were asymptomatic, and it was only identified at the time of their usual restaging. I'm not sure that I'm ready to administer this regimen in place of the standard, which would be radiation therapy for most patients, but I believe that in some situations it could be useful.

4.1

LANDSCAPE: Results from a Phase II Study of Lapatinib (Lap) and Capecitabine (Cape) for Patients with Brain Metastases from HER2-Positive Breast Cancer Before Whole-Brain Radiation Therapy (WBRT)

Response	Cape + lap
CNS objective response (centrally confirmed, n = 35)*	67.4%
Median time to disease progression (n = 44)	5.5 months
CNS site of first progression (n = 43)	73.4%
Extra-CNS site of first progression (n = 43)	7.0%
Concomitant CNS and extra-CNS sites of first progression (n = 43)	11.6%
Median time to WBRT (n = 43)	7.8 months
Select adverse events (Grade 3 or 4)	**n = 45**
Diarrhea	20.0%
Hand-foot syndrome	20.0%
Fatigue	13.3%
Rash	4.4%
Nausea	2.2%

* ≥50% volumetric reduction of CNS lesions

Bachelot TD et al. *Proc ASCO* 2011;**Abstract 509**.

Tracks 5-6

DR LOVE: Would you talk about the results of your Phase II study of afatinib, an irreversible EGFR TKI we've heard a lot about in lung cancer, for patients with HER2-positive mBC progressing after trastuzumab?

DR LIN: As you know, a number of HER2-targeted TKIs exist, and we recently published results from a Phase II study evaluating afatinib in patients with refractory breast cancer who'd received a median of 3 prior lines of HER2-directed therapy in the metastatic setting. The response rate including stable disease was 46% (Lin 2012; [4.2]). Data have also been reported with neratinib, for which a 25% response rate was observed in a similar patient population.

DR LOVE: What about toxicities with these new TKIs? Lapatinib is a bit of a challenge to start with, and neratinib has a reputation of being difficult to tolerate. What about afatinib?

DR LIN: In the afatinib study we published, the rate of Grade 3 diarrhea was 25%. So these agents do carry toxicities with them, probably related to the EGFR effect. These agents are not associated with alopecia, but the diarrhea, although manageable, is a concerning side effect and is different than we would see with T-DM1 or pertuzumab, for example. Some newer HER2-targeted TKIs that are a little further behind in development target HER2 and not EGFR. It is conceivable that they may be better tolerated, although we don't have the efficacy data yet.

4.2

Phase II Study of Afatinib for Patients with HER2-Positive Metastatic Breast Cancer Progressing After Trastuzumab

Response	All treated patients (n = 41)	Evaluable patients (n = 35)
CR + PR + SD	46%	54%
PR	10%	11%
SD	37%	43%
Progressive disease	39%	46%
Median PFS	15.1 weeks	—
Median overall survival	61.0 weeks	—
Select adverse events (n = 41)	**All grades**	**Grade 3**
Diarrhea	90.2%	24.4%
Rash	65.9%	9.8%

CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival

Lin NU et al. *Breast Cancer Res Treat* 2012;133(3):1057-65.

Tracks 8, 10-11

DR LOVE: I also want to ask you about an issue that doesn't get much exposure in terms of inclusion in clinical research — the role of diet and exercise. The ongoing Phase II ABCDE trial at your institution includes a randomization to these interventions. Would you discuss the status of that trial?

DR LIN: Although it's easy to tell patients to "make sure you're not gaining weight and try to exercise more," it's difficult to make lifestyle changes. If we were able to demonstrate that a particular intervention led to better outcomes, you might imagine that this would then be covered by insurance and that people would have better access to it.

The ABCDE trial includes a 2-by-2 randomization. The first randomization is to a low-dose metronomic cyclophosphamide/methotrexate regimen with bevacizumab

versus no chemotherapy/bevacizumab therapy, and the second randomization is to a series of telephone-based counseling sessions on diet interventions versus the diet intervention counseling in combination with counseling to encourage increased exercise.

DR LOVE: What have you observed with patients who've been randomly assigned to the diet and exercise intervention arm?

DR LIN: The patients who have been assigned to the intensive lifestyle intervention have uniformly felt positive about it. I believe that's because they can immediately see the effect. So regardless of whether lifestyle interventions end up improving disease-free survival, as has been previously reported in other studies (Chlebowski 2006), they have already been shown to yield improvements in endurance and decreases in level of fatigue and in overall weight. These are all factors that people can feel immediately.

Track 14

DR LOVE: Would you provide an update on the TAILORx and RxPONDER trials evaluating Onco*type* DX in patients with node-negative and node-positive disease?

DR LIN: We placed a few patients at our institution on the TAILORx trial. It's interesting because it was predicted that TAILORx would encounter difficulty in accruing patients but in fact this trial has exceeded all expectations.

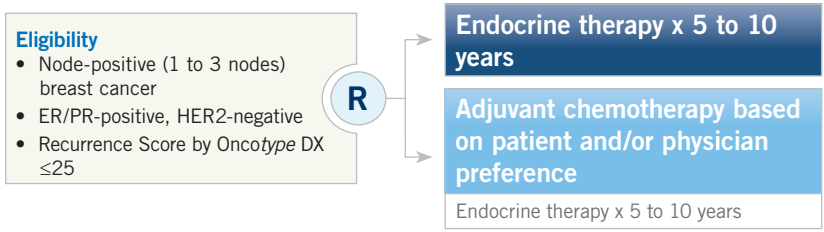
Our institution is also participating in the RxPONDER trial for patients with up to 3 positive nodes (4.3). RxPONDER was designed to anticipate that a number of patients would not accept the randomization, so it was powered to have enough people enter the actual randomization. Some predictions were made of what that rate would be, and so far accrual is going well for the RxPONDER trial. Patients are getting the result and continuing on toward randomization. ■

4.3

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



www.clinicaltrials.gov. Identifier NCT01272037, October 2012.

SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study.** *J Natl Cancer Inst* 2006;98(24):1767-76.

Kurzrock R et al. **Safety, pharmacokinetics, and activity of GRN1005, a novel conjugate of angiopep-2, a peptide facilitating brain penetration, and paclitaxel, in patients with advanced solid tumors.** *Mol Cancer Ther* 2012;11(2):308-16.