INTERVIEW

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Tracks 1-11

Select Excerpts from the Interview

Tracks 1-3, 5

Case discussion

A 44-year-old woman who previously received adjuvant chemotherapy/trastuzumab for HER2-positive, node-positive breast cancer presents with bilateral lung metastases

DR VERMA: This patient completed adjuvant treatment in October 2011, and she recently presented with a cough and shortness of breath that was affecting her ability to climb a flight of stairs in her home. The CT revealed a small right pleural effusion in addition to the lung metastases.

She is an otherwise active person and had bounced back nicely after completing trastuzumab in the adjuvant setting, so in terms of treatment options at this point we were considering standard trastuzumab-based treatment with paclitaxel/trastuzumab,

2.1

CLEOPATRA: A Phase III Trial of Pertuzumab, Trastuzumab and Docetaxel as First-Line Therapy for HER2-Positive Metastatic Breast Cancer

	Ptz + T + D (n = 402)	**Pla + T + D** (n = 406)	HR	*p*-value
Median progression-free survival	18.7 mo	12.4 mo	0.69	NR
Median overall survival	Not reached	37.6 mo	0.66	0.0008

Median follow-up: 30 months
Ptz = pertuzumab; T = trastuzumab; D = docetaxel; Pla = placebo; HR = hazard ratio; NR = not reported

Swain SM et al. *Lancet Oncol* 2013;14(6):461-71.

docetaxel/trastuzumab or vinorelbine/trastuzumab. The data are strongest with docetaxel/trastuzumab/pertuzumab as per the CLEOPATRA study (Swain 2013; [2.1]), so we offered her docetaxel/trastuzumab/pertuzumab or paclitaxel/trastuzumab/pertuzumab. We don't have Phase III data with paclitaxel, but the consensus is that the choice of paclitaxel versus docetaxel is not critical for the dual HER2-targeted therapy to be effective. She chose paclitaxel/trastuzumab/pertuzumab. We started treatment 2 weeks ago, and she seems to be faring well.

DR LOVE: If you could have accessed T-DM1, would you have used it in this case?

DR VERMA: On the EMILIA study patients had to experience recurrence within 6 months of completing adjuvant trastuzumab, so this patient would not fit the criteria to receive T-DM1 according to the protocol. The data with T-DM1 are strongest in the first line if patients have experienced a short disease-free interval (Verma 2012; [2.2]). In the CLEOPATRA trial patients were eligible to enroll as long as the adjuvant trastuzumab was completed 1 year ago and the disease-free interval was 1 year or more. For this reason we chose pertuzumab/trastuzumab/taxane. T-DM1 will be an option for this patient at disease progression.

DR LOVE: What do we know in terms of predictors of response to pertuzumab?

DR VERMA: One would think that HER3 expression would be a predictor of response to pertuzumab, considering that the agent blocks the dimerization of HER2, particularly with HER3. However, that's not the case. Prior trastuzumab is potentially a prognostic marker — patient prognosis is slightly worse if they received prior trastuzumab — but we still have not identified any new predictive biomarkers.

2.2

EMILIA: Results from a Phase III Study of T-DM1 versus Capecitabine and Lapatinib (XL) for HER2-Positive Advanced Breast Cancer

Outcome	**T-DM1**	**XL**	Hazard ratio	*p*-value
Median progression-free survival* (n = 495, 496)	9.6 mo	6.4 mo	0.65	<0.001
Median overall survival† (n = 495, 496)	30.9 mo	25.1 mo	0.68	<0.001
Objective response rate (n = 397, 389)	43.6%	30.8%	—	<0.001

* By independent review; † Second interim analysis results crossed the stopping boundary for efficacy

Verma S et al. *N Engl J Med* 2012;367(19):1783-91.

DR LOVE: Do you have any predictions about what we might see in terms of results from the MARIANNE trial (2.3), which is evaluating T-DM1 with or without pertuzumab versus a taxane/trastuzumab for patients with HER2-positive metastatic breast cancer?

DR VERMA: MARIANNE is a pivotal trial, and we're expecting the results in 2014. The combination pertuzumab/T-DM1 arm is of specific interest in terms of improving outcomes, particularly with regard to progression-free survival and what was already achieved in the CLEOPATRA study (2.1). We will see some indirect comparisons between the T-DM1/pertuzumab arm from MARIANNE and the docetaxel/trastuzumab/pertuzumab arm from CLEOPATRA, but what we're hoping for is a progression-free survival of more than 18.5 months.

DR LOVE: What other trials are exploring pertuzumab and T-DM1, particularly in the adjuvant and neoadjuvant settings?

DR VERMA: The APHINITY adjuvant trial (2.3), which is nearing completion of accrual, is evaluating chemotherapy/trastuzumab versus chemotherapy/trastuzumab/pertuzumab. This is a pivotal study investigating whether a benefit exists with the addition of pertuzumab in the adjuvant setting among patients with early-stage breast cancer.

Additional studies in the neoadjuvant setting are being planned and clarified. What exactly the trial arms will require is still being discussed, but the basic premise is that the studies will evaluate chemotherapy/trastuzumab as the control arm versus chemotherapy/trastuzumab/pertuzumab or T-DM1/pertuzumab.

An important consideration when using a targeted approach among patients who may not be receiving chemotherapy, even in the early-stage setting, is the initial HER2 testing. We must be completely confident that we are dealing with HER2-positive disease, so testing is critical.

DR LOVE: What is your clinical perception of the toxicities with pertuzumab and also with T-DM1?

DR VERMA: The toxicity profile with pertuzumab as reported in the CLEOPATRA trial includes an increased rate of rash and an increased risk of diarrhea. Higher febrile neutropenia rates have also been noted.

In terms of T-DM1, it is one of the most effective and least toxic agents in the breast cancer armamentarium. Patients generally "sail through" treatment and usually don't experience toxicities affecting their quality of life. No nausea, vomiting or hair loss occurs, and patients are not at risk for febrile neutropenia or infection.

2.3 **Key Ongoing Phase III Trials for Patients with HER2-Positive Breast Cancer**

Trial identifier	N	Setting	Treatment arms
APHINITY (NCT01358877)	4,800	Adjuvant	• Chemotherapy + trastuzumab + pertuzumab • Chemotherapy + trastuzumab + placebo
MARIANNE (NCT01120184)	1,095	Metastatic	• Trastuzumab + taxane • T-DM1/placebo • T-DM1/pertuzumab

www.clinicaltrials.gov, September 2013.

The toxicities we need to educate our patients about prior to therapy include thrombocytopenia and the potential for nosebleeds, pneumonitis and liver toxicity. One rare side effect is focal nodular hyperplasia, with which patients experience liver toxicity that does not translate into elevations in liver enzymes. Patients may exhibit signs of portal hypertension, varices, splenomegaly or abdominal discomfort, and when this happens treatment likely should be discontinued. Cases of pneumonitis have been reported, which would also be a reason to discontinue therapy.

Track 9

DR LOVE: What are your thoughts on using mTOR inhibitors with endocrine therapy in patients with endocrine-naïve disease?

DR VERMA: A neoadjuvant study suggested that mTOR is an important pathway in breast cancer even in the context of a treatment-naïve patient population (Baselga 2009). Patients were randomly assigned to neoadjuvant letrozole or letrozole/everolimus. The data indicated that the addition of everolimus to letrozole led to an improvement in response and a reduction in Ki-67 expression compared to letrozole alone.

This provides a rationale for studying everolimus in the early setting in addition to the first-line metastatic setting. At least 3 adjuvant trials are under way evaluating everolimus in the adjuvant setting (2.4). One of the challenges of studying this agent in the adjuvant setting is that patients with hormone receptor-positive disease have an excellent prognosis to begin with. We must identify the appropriate patients who are more at risk of disease recurrence and are more likely to have a better risk-benefit analysis. In most cases the trials include patients with significant nodal involvement or those who have a high Recurrence Score (RS) or other adverse prognostic factors, and that is the correct approach. ■

2.4

Ongoing Adjuvant Trials Evaluating Everolimus-Based Therapy for Patients with Breast Cancer

Trial identifier	Phase	N	Treatment arms
SWOG-S1207 (NCT01674140)	III	3,500	• Endocrine therapy + everolimus x 1 year • Endocrine therapy + placebo x 1 year
NCT01805271	III	1,984	• Endocrine therapy x 3 years → everolimus • Endocrine therapy x 3 years → placebo
NCT00930930	II	145	• Cisplatin/paclitaxel + everolimus • Cisplatin/paclitaxel + placebo

www.clinicaltrials.gov, September 2013.

SELECT PUBLICATIONS

Baselga J et al. **Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer.** *J Clin Oncol* 2009;27(16):2630-7.

Swain S et al. **Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study.** *Lancet Oncol* 2013;14(6):461-71.

Verma S et al. **Trastuzumab emtansine for HER2-positive advanced breast cancer.** *N Engl J Med* 2012;367(19):1783-91.