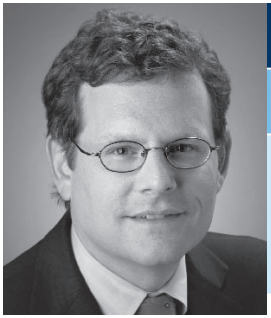

INTERVIEW

Clifford Hudis, MD

Dr Hudis is Chief of the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the data analysis of the BIG 1-98 and ATAC trials presented at SABCS 2010 in relation to CYP2D6 genotyping and clinical outcome in postmenopausal women with early breast cancer?

DR HUDIS: This has been an area of controversy because we have conflicting evidence on the use of CYP2D6 testing to assist with making treatment decisions. The hypothesis that CYP2D6 genotype could predict response to

tamoxifen was sound, but some past studies were positive and others were negative, which left clinicians scratching their heads.

The bottom line is that CYP2D6 status did not allow clinicians to predict with any accuracy which patients did or did not benefit from tamoxifen (Leyland-Jones 2010; Rae 2010). The data sets presented at San Antonio were clean and well-studied, prospectively followed patient populations. This is likely the highest level of evidence we're ever going to acquire, and this is almost a unique resource at this point. I believe this story is over.

Track 8

DR LOVE: Would you discuss the Neo-ALTTO study, evaluating multiple anti-HER2 strategies in the neoadjuvant setting?

DR HUDIS: The Neo-ALTTO study demonstrated that response rates were similar between paclitaxel/lapatinib and paclitaxel/trastuzumab and that the combination of three drugs — trastuzumab/paclitaxel/lapatinib — was associated with the best response (Baselga 2010; [1.1]). The three-drug combination appeared better than paclitaxel/trastuzumab, a factor that suggests the three-drug arm of the ongoing ALTTO trial will be the winner.

Because previous studies of the two anti-HER2 drugs showed activity in patients with heavily pretreated disease that progressed multiple times, in most cases during treatment with trastuzumab, the Neo-ALTTO strategy may be a viable one to increase response in the early-stage setting. However, based on the results of this study, when using a two-drug strategy we have no reason to substitute paclitaxel/lapatinib for paclitaxel/trastuzumab.

One might speculate that the former regimen has less cardiac toxicity, but more gastrointestinal and skin toxicity occurs and nothing indicates that the lapatinib combination is more active.

1.1 **Pathologic Complete Response (pCR) Rates in the Neo-ALTTO Phase III Neoadjuvant Trial of Lapatinib (L), Trastuzumab (T) and the Combination with Paclitaxel (P) in HER2-Positive Primary Breast Cancer**

Response	P + L (n = 154)	P + T (n = 149)	P + L + T (n = 152)
pCR[1]	24.7%	29.5%	51.3%
	p-value: 0.34 (L vs T); 0.0001 (L + T vs T)		
	P + L (n = 150)	P + T (n = 145)	P + L + T (n = 145)
Total pCR[2]	20.0%	27.6%	46.9%
	p-value: 0.13 (L vs T); 0.001 (L + T vs T)		

[1] No invasive cancer in the breast; [2] No invasive cancer in the breast and lymph nodes (excludes 15 patients with nonevaluable nodal status)

Baselga J et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

Track 10

DR LOVE: Can you discuss the results of a second anti-HER2 study, NEOSPHERE, reported at San Antonio?

DR HUDIS: The four arms of the NEOSPHERE trial included neoadjuvant treatment with (1) trastuzumab and docetaxel, (2) pertuzumab and docetaxel, (3) trastuzumab, pertuzumab and docetaxel or (4) an interesting combination of trastuzumab and pertuzumab alone (Gianni 2010; [1.2]).

The results of the NEOSPHERE trial echoed those of the Neo-ALTTO study. The three-drug combination — both antibodies in combination with docetaxel — was associated with the highest in-breast response rate. This result was most clearly observed in the population with ER-negative disease, in which the pathologic complete response (pCR) rate was 63.2 percent. The pCR rate in the patients with ER-positive disease was 26 percent.

Omitting the chemotherapy clearly yielded inferior results. The pCR rate was only six percent for the patients with ER-positive disease who received the two antibodies, and the in-breast response rate for antibody treatment alone was 16.8 percent. The trastuzumab/docetaxel and the pertuzumab/docetaxel arms had respectable response activity but were inferior to the three-drug combination.

1.2

NEOSPHERE Study: Pathologic Complete Response (pCR) in the Breast and Lymph Node Status of Patients Receiving Neoadjuvant Trastuzumab and/or Pertuzumab

	TH (n = 107)	THP* (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node-negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node-positive at surgery	7.5%	6.5%	5.6%	6.3%

T = docetaxel; H = trastuzumab; P = pertuzumab

* *p*-value was significant for THP versus all other arms for each outcome shown

Gianni L et al. San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

Track 13

DR LOVE: Let's talk about new agents in breast cancer. What are your thoughts on the most recently approved treatment, eribulin?

DR HUDIS: Eribulin — a synthetic analog of a compound derived from the sea sponge — is a novel antitubulin agent that is interesting in terms of drug

development. Its approval was based on a clinical trial that randomly assigned patients to salvage treatment with eribulin or investigator's treatment of choice — gemcitabine, capecitabine, vinorelbine, weekly paclitaxel, anthracyclines, hormone therapy or best supportive care. Despite lumping together all those salvage therapies as a comparator, an overall survival advantage was reported in the patients randomly assigned to eribulin (Cortes 2011; [1.3]).

I believe this finding is profound because it indicates that the treatment choices we make, even in the salvage setting, can make a difference. All of our current salvage therapy approaches may be inferior to eribulin.

This trial shows that we should not be dismissive or cavalier in the salvage treatment setting. I believe eribulin deserves a fairly steady place in our treatment algorithm at this point because we don't have many treatments that have been shown to improve survival. ■

1.3

EMBRACE Trial: Eribulin versus Treatment of Physician's Choice (TPC) for Patients with Previously Treated Locally Recurrent or Metastatic Breast Cancer

Endpoint (ITT population)	Eribulin	TPC	Hazard ratio	*p*-value
Median OS (n = 508, 254)	13.1 mo	10.6 mo	0.81	0.041
Median PFS* (n = 508, 254)	3.7 mo	2.2 mo	0.87	0.14
ORR* (CR + PR) (n = 468, 214)	12%	5%	—	0.002
CBR* (CR + PR + SD) (n = 468, 214)	23%	17%	—	—

* Independent review

ITT = intent to treat; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; CBR = clinical benefit rate; SD = stable disease ≥6 months

Cortes J et al. *Lancet* 2011;377(9769):914-23.

SELECT PUBLICATIONS

Baselga J et al. **First results of the NeoALTTO trial (BIG 01-06/EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

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* 2011;377(9769):914-23.

Gianni L et al. **Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized Phase II study ('NeoSphere').** San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

Leyland-Jones B et al. **Outcome according to CYP2D6 genotype among postmenopausal women with endocrine-responsive early invasive breast cancer randomized in the BIG 1-98 trial.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-8**.

Rae JM et al. **Lack of correlation between gene variants in tamoxifen metabolizing enzymes with primary endpoints in the ATAC trial.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-7**.