INTERVIEW

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Tracks 1-10

Select Excerpts from the Interview

Track 3

DR LOVE: What is your perspective on the Phase III CLEOPATRA trial comparing the addition of pertuzumab to trastuzumab and docetaxel as first-line therapy for patients with HER2-positive metastatic breast cancer?

DR CORTES: The CLEOPATRA trial demonstrated that when pertuzumab is added to trastuzumab-based therapy an improvement occurs in all outcomes. Increases were observed in progression-free survival, overall response rate and overall survival, and quality of life improved with no significant increase in toxicity (Swain 2013; [2.1, page 7]; Cortes 2013a).

The hazard ratio for survival with the addition of pertuzumab to trastuzumab/docetaxel was 0.66 in CLEOPATRA, whereas it was 0.80 with the addition of trastuzumab to chemotherapy in the original pivotal trial of trastuzumab (Slamon 2001). So the benefit of adding pertuzumab to trastuzumab/chemotherapy is larger than the original benefit reported with the addition of trastuzumab to chemotherapy, which is amazing.

Tracks 6-7

DR LOVE: Would you discuss the data presented at ASCO 2013 from the Phase III trial comparing eribulin to capecitabine for patients with locally advanced or metastatic breast cancer?

DR CORTES: Eribulin is an antimitotic agent demonstrated to significantly increase overall survival compared to treatment of physician's choice in the late-line setting for patients with metastatic breast cancer (Cortes 2011). It has been considered the standard treatment in that setting.

This recent Phase III trial comparing eribulin to capecitabine was designed to move eribulin up earlier in the metastatic setting for patients who received anthracyclines and taxanes and for whom capecitabine is considered standard therapy. The results showed that eribulin did not improve progression-free or overall survival, the coprimary endpoints of the trial. Even though numerically the hazard ratio for median overall survival favored the eribulin arm, from a statistical point of view the trial was negative (Kaufman 2012). A subgroup analysis of the data at ASCO 2013 reported that in patients with HER2-negative disease and with triple-negative disease, eribulin was superior to capecitabine (Kaufman 2013; [4.1]).

We also presented a study comparing the quality of life for patients receiving eribulin to that of those receiving capecitabine. Overall quality of life was improved with both agents, but it was significantly better with eribulin (Cortes 2013b; [4.2]). I believe that both the antitumor efficacy and side effects of these therapies play a role. When we evaluated the quality of life based on known adverse events associated with these agents, we found that issues related to hair loss favored capecitabine. However, parameters related to gastrointestinal side effects were better with eribulin.

DR LOVE: What were the main side effects observed with eribulin and capecitabine in the Phase III head-to-head trial?

4.1 **Phase III Study of Eribulin versus Capecitabine for Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes**

Median overall survival	Eribulin	Capecitabine	Hazard ratio
Overall (n = 554, 548)	15.9 mo	14.5 mo	0.88*
HER2 status			
HER2-positive	14.3 mo	17.1 mo	0.97
HER2-negative	15.9 mo	13.5 mo	0.84
ER status			
ER-positive	18.2 mo	16.8 mo	0.9
ER-negative	14.4 mo	10.5 mo	0.78
Triple-negative			
Yes	14.4 mo	9.4 mo	0.7
No	17.5 mo	16.6 mo	0.93

* $p = 0.056$

Prespecified exploratory analysis showed that subgroups of patients with HER2-negative ($p = 0.03$), ER-negative ($p = 0.02$) or triple-negative ($p = 0.01$) disease may have a greater benefit in overall survival with eribulin compared to capecitabine.

Kaufman P et al. *Proc ASCO* 2013;**Abstract 1049**.

4.2

Quality of Life for Patients with Locally Advanced or Metastatic Breast Cancer in a Phase III Study of Eribulin versus Capecitabine

- Global health status and overall quality of life scores improved in both arms but significantly more with eribulin than with capecitabine ($p = 0.048$), suggesting subjective treatment benefit.
- Cognitive functioning improved for patients receiving eribulin compared to capecitabine, whereas emotional functioning improved for patients receiving capecitabine compared to eribulin.
- Advantages in parameters linked to gastrointestinal effects (nausea, vomiting and diarrhea) were observed with eribulin, whereas advantages in parameters related to hair loss were observed with capecitabine.

Cortes J et al. *Proc ASCO* 2013b;**Abstract 1050**.

DR CORTES: Compared to other antimitotic agents, eribulin is well tolerated. Myelosuppression is not a big issue for patients who receive eribulin. Alopecia can be a problem with this agent. One of the major side effects with eribulin is neurotoxicity, with Grade 3 to 4 peripheral neuropathy being reported in 8% of patients.

Capecitabine is generally well tolerated. However, 15% to 20% of patients develop Grade 3 hand-foot syndrome, which may require a dose adjustment.

DR LOVE: What are your thoughts on using eribulin for patients with breast cancer in earlier-stage disease?

DR CORTES: In my opinion, eribulin is as good as or better than capecitabine, especially in HER2-negative disease. I would use eribulin for a patient with triple-negative disease as second-line therapy. However, it is not yet approved in that setting. We are also conducting a clinical trial with single-agent eribulin in the neoadjuvant setting to identify which patients would benefit from this therapy (4.3).

4.3

Key Ongoing Phase II Trials Evaluating Eribulin-Based Therapy for Patients with Breast Cancer

Trial identifier	N	Setting	Treatment arms
SOLTI-1007 (NCT01669252)	200	• Neoadjuvant • HER2-negative	• Eribulin
NCT01593020	152	• Neoadjuvant • HER2-negative	• Eribulin → FAC or FEC • Paclitaxel → FAC or FEC
NCT01388647	56	• Neoadjuvant • HER2-positive	• Eribulin + trastuzumab + carboplatin
NSABP-FB-9 (NCT01705691)	50	• Neoadjuvant • HER2-negative	• Eribulin → AC • Paclitaxel → AC
NCT01439282	67	• Adjuvant • ER-positive, HER2-negative	• Eribulin + capecitabine
NCT01427933	141	• Metastatic • HER2-positive	• Eribulin + ramucirumab • Eribulin
E-VITA/GBG 64 (NCT01534455)	80	• Metastatic • HER2-positive	• Eribulin (1.23 mg) + lapatinib • Eribulin (1.76 mg) + lapatinib

F = 5-FU; A = doxorubicin; C = cyclophosphamide; E = epirubicin

www.clinicaltrials.gov, September 2013.

Track 10

DR LOVE: ATLAS, an international Phase III study, and its United Kingdom counterpart, the aTTom trial, randomly assigned women with early breast cancer who had completed 5 years of adjuvant tamoxifen to either continue or stop tamoxifen. Would you comment on the results of these studies?

DR CORTES: One of the most important presentations at ASCO 2013 was the aTTom trial. The results of aTTom in conjunction with the ATLAS trial demonstrated that 10 years of tamoxifen is a better option for patients than 5 years of therapy (Gray 2013; Davies 2013; [4.4]). The aTTom data reported that the absolute benefit in terms of overall survival was approximately 3%. So for some patients 10 years of tamoxifen would be a good option. I would administer 10 years of tamoxifen for patients who are pre- or perimenopausal with high-risk tumors and node involvement. ■

4.4

ATLAS and aTTom Trials: Effect on Breast Cancer Recurrence and Mortality of Continuing Adjuvant Tamoxifen (TAM) to 10 Years versus Stopping at 5 Years

	10 y TAM vs 5 y: **aTTom trial** (n = 6,934 ER+/UK)	10 y TAM vs 5 y: **ATLAS trial*** (n = 10,543 ER+/UK)	10 y TAM vs 5 y: **aTTom and ATLAS combined** (n = 17,477 ER+/UK)
Years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) $p = 0.007$	0.75 (0.63-0.90) $p = 0.002$	0.75 (0.65-0.86) $p = 0.00004$
All years	0.88 (0.74-1.03) $p = 0.1$	0.83 (0.73-0.94) $p = 0.004$	0.85 (0.77-0.94) $p = 0.001$

* Inverse-variance-weighted estimate of the effect in ER-positive disease

- aTTom and ATLAS together provide "proof beyond reasonable doubt" that continuing TAM beyond 5 years reduces recurrence over the following years: No effect in years 5-6, benefit mainly after year 7
- Continuing TAM beyond 5 years also reduces breast cancer mortality: No effect in years 5-9, 25% reduction after year 10
- Main risk: Endometrial cancers (10 y vs 5 y TAM: 2.9% vs 1.3%, $p < 0.0001$)

Gray R et al. *Proc ASCO* 2013;**Abstract 5**; Davies C et al. *Lancet* 2013;381(9869):805-16.

SELECT PUBLICATIONS

Cortes J et al. **Health-related quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer.** *Ann Oncol* 2013a;[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* 2011;377 (9769):914-23.

Kaufman PA et al. **A phase III, open-label, randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.** San Antonio Breast Cancer Symposium 2012;**Abstract S6-6**.

Slamon D et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92.

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.