INTERVIEW

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DR LOVE: The final overall survival results of the CLEOPATRA trial for patients with HER2-positive mBC were recently published (Swain 2015). Would you discuss the rationale for and results of the study, for which you were one of the lead investigators?

DR SWAIN: CLEOPATRA was a Phase III trial that evaluated the addition of pertuzumab to trastuzumab and docetaxel as first-line therapy. Previous data demonstrated synergy with trastuzumab and taxanes. Docetaxel was chosen as chemotherapy because it was a worldwide study. We experienced a lot of difficulty with accrual in the United States because of the docetaxel backbone, which is usually not administered in metastatic disease. Eventually, we were able to accrue more than 800 patients, with only 16% of them in the United States.

I was surprised at how impressive the results were, with a 6-month PFS benefit (Baselga 2012). The median overall survival was 56.5 months on the pertuzumab arm versus approximately 41 months on the control arm, which is incredible (Swain 2015). What I see from my experience and hear from colleagues is that the response rates are fantastic. So the results are holding up in practice also.

DR LOVE: How do you approach a patient who experiences early relapse after receiving a taxane and trastuzumab in your practice outside a trial setting?

DR SWAIN: I would offer pertuzumab and trastuzumab with vinorelbine, which is an active regimen. T-DM1 may also be reasonable but may not elicit a response in these patients. I believe for patients with disease that is resistant to trastuzumab, other agents should be considered.

DR LOVE: What does pertuzumab add in terms of toxicity?

DR SWAIN: Diarrhea occurs in approximately 60% of patients, and Grade 3 or 4 diarrhea, which can lead to dehydration, is observed in about 10% of patients. Dermatologic toxicity occurs in 25% of patients, but I haven't observed many cases. Rash can occur frequently with docetaxel, but the incidence is higher in patients who also receive pertuzumab. The incidence of febrile neutropenia is increased with pertuzumab, especially in the Asian population, in whom it occurs approximately 25% of the time.

DR LOVE: MARIANNE was a Phase III trial that evaluated T-DM1 with or without pertuzumab versus trastuzumab and a taxane for the first-line treatment of HER2-positive mBC. Would you talk about the design and results of the study?

DR SWAIN: This trial was designed before the CLEOPATRA data were presented, but considering those results in hindsight, it would have been better for pertuzumab to be added to the control arm of trastuzumab with a taxane. The findings were disappointing, with no difference between the arms. T-DM1 with pertuzumab was noninferior to T-DM1 alone or to trastuzumab/taxane, but it certainly wasn't superior as we had hoped it would be (Ellis 2015; [2.1]).

DR LOVE: What's your experience with T-DM1 in terms of the tolerability?

DR SWAIN: T-DM1 is well tolerated in most patients, the major toxicity being elevated liver enzymes and a decrease in platelets. These side effects may require dose reductions. I had a patient who was unable to tolerate lapatinib/capecitabine but experienced an unbelievable response to T-DM1. So in many patients it works well because the quality of life is good with low toxicity.

Track 8

DR LOVE: What are your thoughts on the APT trial investigating adjuvant paclitaxel and trastuzumab for HER2-positive breast cancer?

DR SWAIN: Trastuzumab is known to be effective in the adjuvant setting, but many patients don't need intensive chemotherapy. So the Dana-Farber group conducted a trial in which patients with small, node-negative, HER2-positive tumors received adjuvant paclitaxel in combination with trastuzumab. The results were outstanding. The 3-year rate of disease-free survival was 99% for patients with ER-negative tumors and approximately 98% for those with ER-positive ones (Tolaney 2015). So I believe that adjuvant paclitaxel and trastuzumab is an option for some patients.

2.1

MARIANNE: Results of a Phase III Study of T-DM1 with or without Pertuzumab versus Trastuzumab with a Taxane as First-Line Therapy for HER2-Positive Metastatic Breast Cancer

Efficacy	HT (n = 365)	T-DM1 (n = 367)	T-DM1 + P (n = 363)
Median progression-free survival	13.7 mo	14.1 mo	15.2 mo
Stratified HR versus HT	—	0.91	0.87
Overall response rate	67.9%	59.7%	64.2%
Median duration of response	12.5 mo	20.7 mo	21.2 mo
Select adverse events	**HT (n = 353)**	**T-DM1 (n = 361)**	**T-DM1 + P (n = 366)**
Alopecia	59.8%	6.6%	9.0%
Diarrhea	48.7%	25.2%	48.1%
Peripheral neuropathy	28.0%	13.3%	17.8%
Neutropenia	22.7%	11.4%	8.7%

HT = trastuzumab/taxane; P = pertuzumab

Median overall survival was not yet reached for any arm.

Ellis P et al. *Proc ASCO* 2015;**Abstract 507**.

As a follow-up to that study, the ATEMPT trial is evaluating T-DM1 versus paclitaxel and trastuzumab for Stage I, HER2-positive breast cancer. I believe it's a great study. Some patients with limited disease don't need the aggressive chemotherapy that we administer. At ASCO 2015, Nadia Harbeck presented a trial that assessed 12 weeks of neoadjuvant T-DM1 with or without endocrine therapy for hormone receptor–positive, HER2-positive early breast cancer. They reported high pCR rates (Harbeck 2015; [2.2]). So those data support the concept of using T-DM1 for patients with a lower risk of recurrence in the adjuvant setting.

2.2

ADAPT: Results of a Phase II Trial of Neoadjuvant T-DM1 with or without Endocrine Therapy (ET) in ER-Positive, HER2-Positive Early Breast Cancer

	T-DM1 (n = 37)	T-DM1 + ET (n = 48)	Trastuzumab + ET (n = 45)
Efficacy			
Pathologic complete response	40.5%	45.8%	6.7%
Select AEs (any grade)	**T-DM1 (n = 37)**	**T-DM1 + ET (n = 48)**	**Trastuzumab + ET (n = 45)**
AST increase	19%	10%	0%
ALT increase	22%	6%	2%
Hepatotoxicity	3%	4%	0%
Thrombocytopenia	30%	15%	4%

AEs = adverse events

Harbeck N et al. *Proc ASCO* 2015;**Abstract 506**.

Tracks 11-13

DR LOVE: What are your thoughts on the ability of the Breast Cancer Index assay to predict the risk of recurrence up front and after 5 years of adjuvant endocrine therapy, and do you use it in practice?

DR SWAIN: The data with the Breast Cancer Index and its ability to predict the risk of distant recurrence appear to be good (Sgroi 2013). I have recently started using the assay to determine whether to continue endocrine therapy beyond 5 years. Some patients have small, low-risk disease with negative nodes and a low Onco*type* DX Recurrence Score. In those patients it is beneficial to attempt to determine whether continuing hormonal therapy for 10 years makes sense.

DR LOVE: Do you use the Onco*type* DX assay for decision-making in the front-line setting?

DR SWAIN: I order it for patients who have node-negative disease and for some with node-positive disease. I recently had a patient with a small ER-positive, PR-negative, node-negative tumor and an intermediate Onco*type* DX Recurrence Score of 25.

Tumors that are luminal B subtype and ER-positive, PR-negative may respond better to chemotherapy. So I recommended chemotherapy for this patient. If patients have node-negative disease, I generally administer docetaxel/cyclophosphamide.

DR LOVE: Would you comment on the use of next-generation sequencing for patients with breast cancer?

DR SWAIN: I believe we are at the tip of the iceberg in terms of using next-generation sequencing. Eventually we will be doing it for all patients. Currently in our group we're developing a consensus on which patients we should order it for. One example would be patients who have metaplastic breast cancer who don't experience a response to chemotherapy. I've ordered it in the adjuvant setting for a patient who had many positive nodes. It indicated that an mTOR inhibitor might be beneficial, which pointed to the adjuvant everolimus trial. It may be especially useful for patients who are experiencing relapse.

I would like to see us ordering next-generation sequencing for all patients. It is expensive, but we can learn something about the different mutations. Even though they may not be "actionable" now, this information will be helpful to us in the future. ■

SELECT PUBLICATIONS

Baselga J et al. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Sgroi D et al. **Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population.** *Lancet Oncol* 2013;14(11):1067-76.

Swain SM et al; CLEOPATRA Study Group. **Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer.** *N Engl J Med* 2015;372(8):724-34.

Tolaney S et al. **Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.** *N Engl J Med* 2015;372(2):134-41.

Tolaney S et al. **A Phase II study of adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.** San Antonio Breast Cancer Symposium 2013;**Abstract S1-04**.