INTERVIEW

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Tracks 1-13

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Track 2 Overview of tolerability and efficacy of T-DM1 in mBC

Track 3 Rationale for the ongoing NSABP-B-50-I (KATHERINE) study: A Phase III trial of T-DM1 versus trastuzumab as adjuvant therapy for patients with HER2-positive BC who have residual tumor in the breast or axillary nodes after neoadjuvant treatment

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Select Excerpts from the Interview

Tracks 4-5

DR LOVE: What are your thoughts about the new ASCO guidelines that recommend first-line therapy with the CLEOPATRA regimen of chemotherapy/trastuzumab/pertuzumab followed by second-line T-DM1 for patients with advanced HER2-positive breast cancer?

DR CROWN: First-line therapy with chemotherapy/trastuzumab/pertuzumab followed by second-line T-DM1 makes great sense. The guideline supports the available data. The more generic story that needs to be told is that the circumstantial evidence and, indeed, the trial-based evidence for continuing anti-HER2 therapy beyond first- and second-line treatment is getting stronger. However, in some parts of the world only 1 line of anti-HER2 therapy is approved.

Clearly the current and cleanest data for first-line therapy suggest that for patients for whom the chemotherapy backbone is appropriate, the right anti-HER2 therapy is

the combination of trastuzumab with pertuzumab. As second-line therapy, T-DM1 has been compared to capecitabine/lapatinib and found to be better and safer (Verma 2012).

DR LOVE: Where does lapatinib, particularly in combination with trastuzumab, a nonchemotherapy-based regimen, fit into the treatment sequence, especially for patients who would like to have a chemotherapy break or those who are ineligible for chemotherapy?

DR CROWN: It's a shame that a good, clean first-line study of chemotherapy/trastuzumab with or without lapatinib was not conducted early on, because the body of circumstantial evidence would suggest synergy between the 2 agents, which is clinically relevant. A study of lapatinib with or without trastuzumab for patients with trastuzumab-refractory HER2-positive disease indicated that trastuzumab continuation in combination with lapatinib was beneficial (Blackwell 2010).

This means that in addition to the individual benefit of each drug, synergy occurs when they are used together. For this reason, an ongoing European trial is evaluating chemotherapy and trastuzumab with or without lapatinib (NCT01526369). Even though the increasing availability of pertuzumab will complicate the completion of that trial, pertuzumab is still not available in many jurisdictions.

In most countries, the regulatory approval for lapatinib resides on its use with capecitabine. Some patients who may have received prior capecitabine may be ineligible for lapatinib/capecitabine. However, I have administered the combination of the 2 anti-HER2 therapies without chemotherapy and have seen patients experience a more prolonged degree of disease control.

DR LOVE: ASCO clinical practice guidelines also state that patients with advanced HER2-positive breast cancer and brain metastases should receive appropriate local and systemic therapy. For those receiving anti-HER2 therapy whose systemic disease is not progressing at the time of diagnosis of brain metastases, ASCO recommends that the systemic therapy should not be switched (Ramakrishna 2014). What would be your treatment approach for a patient who achieves a complete response after receiving the CLEOPATRA regimen in the first-line setting but develops brain metastases?

DR CROWN: I would treat the brain metastasis locally on its own merits, either with stereotactic radiosurgery or whole brain radiation therapy, depending on the anatomy of the disease. In general I tend to continue the trastuzumab and, if further problems arise, I add lapatinib.

Tracks 7, 9

DR LOVE: How do you typically use everolimus, which was approved on the basis of the BOLERO-2 trial that evaluated everolimus in combination with exemestane for patients with metastatic breast cancer (3.1)? Do you typically combine it with exemestane only or with other hormonal therapies?

DR CROWN: At this point the available data support its use with an aromatase inhibitor. I'm not particularly concerned about which aromatase inhibitor is selected. I believe that will often be a function of what the patient has been exposed to in the adjuvant setting. Also, issues of habit can arise on the part of the treating oncologist.

3.1

BOLERO-2: A Phase III Trial of Exemestane and Everolimus in ER/PR-Positive Metastatic Breast Cancer Refractory to Nonsteroidal Aromatase Inhibitors

Clinical outcome	Exemestane + everolimus (n = 485)	Exemestane + placebo (n = 239)	Hazard ratio	*p*-value
Median PFS (central assessment)	11.0 mo	4.1 mo	0.38	<0.0001
Median PFS (investigator assessment)	7.8 mo	3.2 mo	0.45	<0.0001
ORR (central assessment)	12.6%	2.1%	—	—
Median overall survival*	31.0 mo	26.6 mo	0.89	0.14
	Exemestane + everolimus (n = 482)		Exemestane + placebo (n = 238)	
Select adverse events	All	Grade 3 or 4	All	Grade 3 or 4
Stomatitis	56%	8%	11%	1%
Fatigue	37%	4%	27%	1%
Cough	22%	1%	11%	0%
Dyspnea	18%	4%	9%	<2%
Pneumonitis	12%	3%	0%	0%

PFS = progression-free survival; ORR = overall response rate

Baselga J et al. *N Engl J Med* 2012;366(6):520-9; Yardley DA et al. *Adv Ther* 2013;30(10):870-84; * Piccart M et al. *Proc European Breast Cancer Conference* 2014;**Abstract LBA1**.

DR LOVE: Would you discuss your clinical experience with everolimus?

DR CROWN: It's so nice to be able to tell patients that they don't need chemotherapy yet and that we can try something else first. Many of my patients have experienced excellent control with everolimus, some with 10 or more months of disease control, clear-cut shrinkage and improvement in quality of life for those with symptomatic pulmonary and other metastases. It can be a useful treatment. Patients tend to know they're receiving everolimus compared to an aromatase inhibitor only. Stomatitis and fatigue are common side effects.

Track 8

DR LOVE: What are your thoughts on the efficacy and safety of the investigational CDK4/6 inhibitor palbociclib as first-line therapy for patients with metastatic breast cancer?

DR CROWN: I've been involved with palbociclib in recent years. Data from the Phase II PALOMA-1 trial of letrozole with or without palbociclib for patients with hormone receptor-positive, HER2-negative metastatic breast cancer are highly provocative and staggering (Finn 2014; [3.2]).

The progression-free survival doubled and a higher response rate was observed with the addition of palbociclib. These results have led to a large-scale randomized Phase III trial (3.3). Palbociclib is not toxic. It's a mild agent, and it's unlikely that we'll have much difficulty with it. ■

3.2 PALOMA-1: Final Results of a Phase II Study of Letrozole (L) with or without the CDK4/6 Inhibitor Palbociclib (P) as First-Line Therapy for ER-Positive, HER2-Negative Metastatic Breast Cancer (mBC)

	P + L	L alone	Hazard ratio	*p*-value
Median PFS	20.2 mo	10.2 mo	0.488	0.0004
Median OS	37.5 mo	33.3 mo	0.813	0.2105
Best ORR*	43%	33%	NR	NR

PFS = progression-free survival; OS = overall survival; ORR = overall response rate; NR = not reported

- The most common adverse events on the P + L arm were neutropenia, leukopenia, fatigue and anemia.

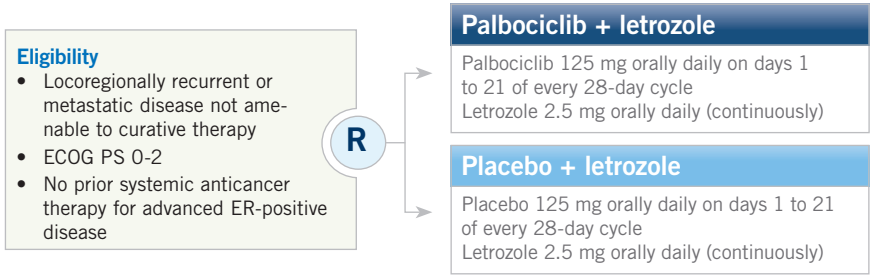
Conclusions: "P + L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P + L in this same mBC population is ongoing."

Finn RS et al. *Proc AACR* 2014;**Abstract CT101**; * Goodman A. *The ASCO Post* 2014;5(7).

3.3 PALOMA-2: A Phase III Trial Evaluating the Oral CDK4/6 Inhibitor Palbociclib with Letrozole versus Placebo with Letrozole as First-Line Therapy for Postmenopausal Patients with ER-Positive, HER2-Negative Advanced Breast Cancer

Protocol ID: NCT01740427

Target Accrual: 650



www.clinicaltrials.gov. Accessed October 2014.

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Blackwell KL et al. **Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer.** *J Clin Oncol* 2010;28(7):1124-30.

Finn RS et al. **Results of a randomized Phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC).** San Antonio Breast Cancer Symposium 2012;**Abstract S1-6**.

Piccart M et al. **Everolimus plus exemestane for hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (BC): Overall survival results from BOLERO-2.** *Proc European Breast Cancer Conference* 2014;**Abstract LBA1**.

Ramakrishna N et al. **Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline.** *J Clin Oncol* 2014;32(19):2100-8.

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