INTERVIEW

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Select Excerpts from the Interview

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DR LOVE: What is known about the synergy of the combination of the anti-HER2 antibodies pertuzumab and trastuzumab for the treatment of HER2-positive breast cancer?

DR BASELGA: Pertuzumab in combination with trastuzumab is far more effective than trastuzumab alone. These agents target different mechanisms of HER2 activation. Trastuzumab has at least 3 well-defined mechanisms of action. First, it is effective in preventing ligand-independent HER2 receptor activation. Second, it can stimulate an antibody-dependent cellular cytotoxicity response against the tumor. Third, internalization of the trastuzumab-HER2 complex causes downregulation of HER2 on the cell surface.

1.1

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.

Pertuzumab binds to a different HER2 epitope than trastuzumab. It binds to the HER2 dimerization domain and blocks HER2/HER3 heterodimerization. HER2/HER3 heterodimers are the most potent signaling duet in breast cancer. Studies have shown that blockade with both anti-HER2 antibodies in combination with chemotherapy is highly effective.

The Phase III CLEOPATRA trial, which studied the effect of adding pertuzumab to trastuzumab/docetaxel as first-line therapy for patients with HER2-positive metastatic breast cancer, was practice changing. It demonstrated a significant improvement not only in progression-free survival but also in overall survival (Swain 2013; [1.1]). The combination is extremely well tolerated. Minimal additional side effects arise from adding pertuzumab to trastuzumab, although side effects such as rash and diarrhea may be observed in some patients.

DR LOVE: What about the pertuzumab/trastuzumab regimen in the second-line setting and beyond?

DR BASELGA: A Phase II study of pertuzumab added to trastuzumab without chemotherapy for patients who were experiencing disease progression while receiving trastuzumab reported promising results. A clinical benefit rate of 50% and a response rate of 25% were observed (Baselga 2010). A cohort of patients who received pertuzumab alone experienced minimal response. Reintroduction of trastuzumab for patients who experienced disease progression while receiving pertuzumab resulted in a response rate of about 20% (Cortes 2012).

This clearly indicates that the combination of pertuzumab and trastuzumab is more active than monotherapy. One can hypothesize that dual HER2 blockade will be effective across the disease spectrum in the first line, second line and beyond.

DR LOVE: What chemotherapy do you believe should be administered in combination with pertuzumab and trastuzumab?

DR BASELGA: Currently we have data only with the combination of pertuzumab/trastuzumab and taxanes. At Memorial we use paclitaxel. However, I believe that other chemotherapies can also be effective in combination with the anti-HER2 antibodies. It would depend on the preference of the patient and physician.

DR LOVE: You are the chair of the Phase III APHINITY trial, which randomly assigns patients to chemotherapy and trastuzumab or chemotherapy and trastuzumab/pertuzumab in the adjuvant setting (1.2). Any comments on this critical trial?

1.2 **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, July 2013.

DR BASELGA: The study is enrolling patients quickly, but it will take a couple of years to obtain the data. The improvement in survival is so significant with trastuzumab/pertuzumab and chemotherapy in first-line metastatic disease that I believe it will be magnified in the adjuvant disease setting.

Tracks 7-9

DR LOVE: Do you believe we will be able to develop a tumor profile that would indicate which HER2-positive tumors are exquisitely sensitive to targeted therapies without chemotherapy?

DR BASELGA: I believe we will identify a patient population that does not need chemotherapy. We know from the NEOSPHERE data (Gianni 2012) and, most important, from a CLEOPATRA biomarker study that phosphatidylinositol 3-kinase (PI3K) is a major prognostic indicator of response to anti-HER2 therapies (Baselga 2012; [1.3]). PI3K is downstream of HER2, and if the gene is mutated the tumor is less sensitive to inhibition of HER2 upstream. Higher levels of HER2 and HER3 correlate with greater benefit. So I am optimistic that we will develop a signature of HER2 dependency.

DR LOVE: What role do you envision for PI3K inhibitors in the treatment of breast cancer?

DR BASELGA: PI3K is one of the next exciting targets in breast cancer. PI3K mutations are observed in approximately 25% of HER2-positive breast tumors and 40% of

1.3 **Biomarker Analysis in the CLEOPATRA Study: Shorter Median Progression-Free Survival and Maintained Treatment Effect with Mutated PIK3CA**

	Median progression-free survival (mo)		
PIK3CA status	**Ptz + T + D**	**Pla + T + D**	Hazard ratio
Mutated (n = 86, 90)	12.5	8.6	0.64
Wild type (n = 190, 191)	21.8	13.8	0.67
Overall (n = 402, 406)	18.5	12.4	0.62

Ptz = pertuzumab; T = trastuzumab; D = docetaxel; Pla = placebo

Baselga J et al. San Antonio Breast Cancer Symposium 2012;**Abstract S5-1**.

ER-positive, HER2-negative tumors. About 8% of patients with triple-negative cancer also have the mutation.

Targeting the PI3K pathway in breast cancer occurs in 3 ways. Agents that target mTOR, which is downstream of PI3K/AKT, comprise 1 class of PI3K inhibitors. The second class of compounds is the pan-PI3K inhibitors, which block all 4 subunits of the enzyme. BKM120 and GDC-0941 are agents in this class that are in clinical development. A third class of compounds, the PI3K-alpha inhibitors, inhibit only the alpha subunit that is mutated in breast cancer. In the Phase I setting we have reported a high response rate for patients with metastatic disease after therapy with PI3K-alpha inhibitors (Juric 2012). Response rates are 5 times higher than with mTOR inhibitors.

In the future we should be able to identify patients up front who harbor PI3K mutations and offer them therapy with PI3K-alpha inhibitors. These compounds are moving fast in clinical development, and Phase II and Phase III trials should start soon.

DR LOVE: Would you talk about your recent paper evaluating the combination of PI3K and PARP inhibitors in triple-negative breast cancer (Ibrahim 2012)?

DR BASELGA: In triple-negative breast cancer PI3K is required for DNA repair. We hypothesized that inhibiting PI3K would induce DNA damage. The study reported that when xenografts from patients with triple-negative breast cancer were exposed to PI3K inhibitors, a marked increase in DNA damage occurred. We found that PI3K inhibition resulted in a major decrease in the levels of BRCA1 and BRCA2, resembling BRCA1/2-deficient tumors.

This suggested that the combination of PI3K and PARP inhibitors would be effective. When we evaluated the combination in animal models, we found noticeable suppression of the growth of aggressive tumors. A Phase I trial combining the PARP inhibitor olaparib with the PI3K inhibitor BKM120 for patients with triple-negative breast cancer is ongoing, and the early data are promising (NCT01623349).

Tracks 10-11

DR LOVE: What are your thoughts on the recently approved agent ado-trastuzumab emtansine (T-DM1), and how do you see it being used in practice?

DR BASELGA: T-DM1 is trastuzumab that is linked to a derivative of maytansine, which is a potent antimetabolite. When the trastuzumab-maytansine complex selectively enters the tumor cell expressing HER2, the maytansine is released and kills that cell. So T-DM1 is appealing, and clinical data with it show impressive results (1.4). The Phase III EMILIA study comparing T-DM1 to the second-line combination of lapatinib and capecitabine demonstrated that T-DM1 was far superior with fewer side effects (Verma 2012).

The big question is, how will we treat HER2-positive breast cancer with all the options we have, namely trastuzumab, pertuzumab, T-DM1 and lapatinib? Although some physicians may consider using T-DM1 as first-line therapy, the data from the EMILIA study indicated that it was superior to approved therapy in the second-line setting.

In the first-line setting we have trastuzumab and pertuzumab with docetaxel. Although it may be true that this combination is more toxic than T-DM1, docetaxel is administered for a median of only 6 cycles. After that patients can receive pertuzumab/

trastuzumab for many months without any significant side effects. So currently I would administer pertuzumab with trastuzumab in the first-line setting, and I would wait until disease progression to use T-DM1.

DR LOVE: Would you comment on the Phase III MARIANNE trial, which is evaluating T-DM1 with or without pertuzumab versus trastuzumab and a taxane for patients with HER2-positive metastatic breast cancer?

DR BASELGA: This ongoing Phase III study is evaluating T-DM1 in the first-line setting for patients with HER2-positive metastatic breast cancer (1.2, page 5). The combination of T-DM1 with pertuzumab and without chemotherapy is exciting. This would offer the possibility of first-line treatment without chemotherapy for patients with metastatic HER2-positive disease. ■

1.4

T-DM1 and the Promise of Antibody-Drug Conjugates

"The pharmacologic properties of trastuzumab emtansine that appear to have been confirmed by this trial [EMILIA] are impressive. Objective evidence of tumor shrinkage indicates, as previously reported in animal models, that HER2 receptor number and function remain intact in most patients in whom clinical resistance to trastuzumab has developed, allowing specific binding of the trastuzumab emtansine conjugate (T-DM1). The remarkable rate of breast-cancer regressions observed at sites of visceral metastases suggests, as originally hypothesized, that the cytotoxic maytansinoid portion of the conjugate is delivered intracellularly at sufficient concentrations to produce cell death (and consequent tumor shrinkage) consistent with mitotic catastrophe, rather than inducing the cytostasis commonly associated with single-agent trastuzumab. The beauty of T-DM1 is that conjugate formation does not preclude the antibody-dependent cellular cytotoxicity or HER2-neutralizing activity of the antibody; thus, T-DM1 retains the functions of trastuzumab and adds the effects of a potent cytotoxic drug."

Teicher BA, Doroshow JH. *N Engl J Med* 2012;367(19):1847-8.

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