Targeting the HER Pathways

The human epidermal growth factor receptor (HER) family has four members: HER1, HER2, HER3 and HER4. These four receptors interact via complex signal transduction pathways, which provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target the different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

ECOG-1100: INTERIM EFFICACY DATA FROM PHASE I/II STUDY OF TRASTUZUMAB AND GEFITINIB IN PATIENTS WITH HER2-OVEREXPRESSING METASTATIC BREAST CANCER

Parameter	Prior chemotherapy (n=8)	No prior chemotherapy (n=28)
Complete response	0	1
Partial response	0	1
Stable disease (24 weeks)	0	7
Progressive disease	8*	11
Time to progression	2.5 months 95% CI, 1.9-2.8 months	2.9 months 95% CI, 2.3-5.9 months

* All patients progressed within 12 weeks.

Conclusion: "At a planned interim analysis, the PFS did not meet predetermined statistical endpoints required for study continuation. Moreover, the observed TTP appears shorter than that previously reported for trastuzumab alone, suggesting the possibility of an antagonistic interaction between trastuzumab and gefitinib. Preliminary correlative studies using HER2-overexpressing br ca cell lines and eTag fluorescent antibody-based assays suggest that treatment with both trastuzumab and gefitinib but not each alone induce phosphorylation of HER3 (erbB3). Whether this is a plausible mechanism of escape that can explain the poor efficacy of the combination is under active investigation. These results do not support the further use of this combination and have implications for other trials using trastuzumab and EGFR TK inhibitors simultaneously." [Citations omitted]

SOURCE: Arteaga CL et al. **ECOG1100: A phase I-II study of combined blockade of the erbB receptor network with trastuzumab and gefitinib ('Iressa') in patients (pts) with HER2-overexpressing metastatic breast cancer (met br ca).** Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 25.

COMPLETE DISAPPEARANCE OF ER+/HER2+ BREAST CANCER XENOGRAFTS WITH THE COMBINATION OF GEFITINIB, TRASTUZUMAB AND PERTUZUMAB

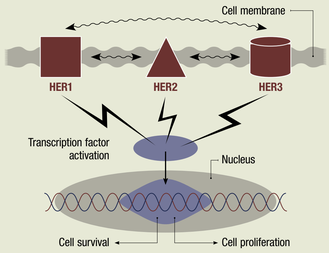
Blockade of HER family signaling	
Agent	**Dimer pair**
Gefitinib	HER1/HER2 HER1/HER3
Trastuzumab	HER2/HER2
Pertuzumab	HER1/HER2 HER2/HER3

Effect of HER family inhibitor on tamoxifen-stimulated growth	
Agents	**Complete response**
Tamoxifen + pertuzumab	5/18
Tamoxifen + pertuzumab + trastuzumab	12/18
Tamoxifen + pertuzumab + trastuzumab + gefitinib	18/20

Conclusion: "Growth factor receptor inhibitors cooperate through distinct, yet complementary, mechanisms to convey a potent HER2 signaling blockade. Combination treatment blocks crosstalk with ER to restore Tam antagonist effect on ER, and together with Tam eradicate MCF7/HER218 tumors. Because growth of these tumors seems to depend mainly on ER and EGFR/HER2 pathways, complete targeted disruption of these pathways can achieve remarkable antitumor activity deserving a clinical trial."

SOURCE: Arpino G et al. **Complete disappearance of ER+/HER2+ breast cancer xenografts with the combination of gefitinib, trastuzumab, and pertuzumab to block HER2 cross-talk with ER and restore tamoxifen inhibition.** Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 23.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (HER) SIGNALING



The HER signal transduction pathways are complex. The HER1, HER2 and HER3 receptors are all members of the HER family. HER1 is also known as the epidermal growth factor receptor. The various components of the HER pathways interact with each other. It is these interactions, or "crosstalk," that may provide multiple approaches for interfering with these signals and inhibiting cancer.

ADDITIONAL TRIALS OF COMBINED BLOCKADE OF THE HER RECEPTOR NETWORK REPORTED AT SABCS 2004

Author/abstract no.	Phase of trial	N	Eligibility	Agent(s)
Blackwell KL/302[1]	NR	58	Trastuzumab-refractory metastatic breast cancer	Lapatinib
Burris III HA/3043[2]	I	26	Advanced or metastatic breast cancer	Lapatinib + trastuzumab
Pegram MD/3039[3]	I	9	Recurrent or metastatic breast cancer	Bevacizumab + trastuzumab

SOURCES: [1] Blackwell KL et al. **Determining molecular phenotypes of metastatic breast cancer that respond to the small molecule inhibitor of ErbB1 and ErbB2, lapatinib (GW572016).** *Proc SABCS* 2004;Abstract 302.

[2] Burris III HA et al. **A phase I, open-label study of the safety, tolerability and pharmacokinetics of lapatinib (GW572016) in combination with trastuzumab.** *Proc SABCS* 2004;Abstract 3043.

[3] Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** *Proc SABCS* 2004;Abstract 3039.

SELECT PUBLICATIONS

Arpino G et al. **Complete disappearance of ER+/HER2+ breast cancer xenografts with the combination of gefitinib, trastuzumab, and pertuzumab to block HER2 cross-talk with ER and restore tamoxifen inhibition.** *Proc SABCS* 2004;Abstract 23.

Arteaga CL et al. **ECOG1100: A phase I-II study of combined blockade of the erbB receptor network with trastuzumab and gefitinib ('Iressa') in patients (pts) with HER2-overexpressing metastatic breast cancer (met br ca).** *Proc SABCS* 2004;Abstract 25.

Badache A, Hynes NE. **A new therapeutic antibody masks ErbB2 to its partners.** *Cancer Cell* 2004;5(4):299-301.

Blackwell KL et al. **Determining molecular phenotypes of metastatic breast cancer that respond to the small molecule inhibitor of ErbB1 and ErbB2, lapatinib (GW572016).** *Proc SABCS* 2004;Abstract 302.

Burris HA 3rd. **Dual kinase inhibition in the treatment of breast cancer: Initial experience with the EGFR/ErbB-2 inhibitor lapatinib.** *Oncologist* 2004;9 (Suppl 3):10-5.

Burris III HA et al. **A phase I, open-label study of the safety, tolerability and pharmacokinetics of lapatinib (GW572016) in combination with trastuzumab.** *Proc SABCS* 2004;Abstract 3043.

Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab**. *Proc SABCS* 2003; Abstract 24.

Nahta R et al. **The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells.** *Cancer Res* 2004; 64(7):2343-6.

Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** *Proc SABCS* 2004;Abstract 3039.

Spector N et al. **The ErbB2 pathway in breast cancer: Best approaches for maximum efficacy.** *Proc SABCS* 2004;Abstract MS3-4.

Yarden Y et al. **Molecular approach to breast cancer treatment.** *Semin Oncol* 2004;31(5 Suppl 10):6-13.

OVERVIEW OF HER2 BIOLOGY

The human epidermal growth factor receptor (HER) family includes four members — HER1, HER2, HER3 and HER4. These receptors interact with and provide signals to cells concerning their biologic behavior. Unlike HER2, the other receptors have ligands that bind to them directly. The most probable explanation for HER2's lack of direct ligand binding is that HER2 is the "driver" of signaling for all members of the HER family. For example, ligands bind to HER1, but rely on HER2 to transmit and amplify their signal. The HER family is analogous to a stereo system with a compact disc, tape and DVD player — each playing different types of media. The CDs, tapes and DVDs are like ligands. The cell can "listen" to several types of ligands, but central to the function of the stereo system is the amplifier. HER2 is equivalent to the amplifier. When the HER2 receptor is overexpressed, the "volume" is turned all the way up on the stereo. This causes breast cancer cells to proliferate rapidly.

— Mark D Pegram, MD

ECOG-1100: INTERIM ANALYSIS

The interim analysis of ECOG-1100 suggests no benefit from combining trastuzumab with gefitinib. In addition, the time to progression in patients treated with the combination was shorter than reported with trastuzumab alone, although not a straight comparison. These data highlight the fact that robust preclinical data do not always predict clinical trial results. I know this combination is being used *ad hoc* in the community, and that needs to be re-examined. This analysis has prompted some questions in the ECOG Breast Core Committee. For example, could we have anticipated these results, avoiding the need for a two-year Phase II study? I speculate that if we had done this in a presurgical setting, like Dr Chang's neoadjuvant trial with single-agent trastuzumab, we might have concluded that this longer study would not be worthwhile.

In an effort to identify the rational partners of trastuzumab, how do we make certain these combinations are at least equivalent or better than trastuzumab alone? At ECOG, partly because of the ECOG-1100 data, we are contemplating a clinical trial plan to identify trastuzumab partners that would not interfere with the overwhelming choice in the community for patients with HER2-positive, metastatic breast cancer, which is basically trastuzumab and chemotherapy. The choice of a partner would be driven by basic science and safety, using time to progression as an endpoint. We have explored the possibility of using bevacizumab as our next partner with trastuzumab.

— Carlos Arteaga, MD

PAN-HER2 INHIBITION

Work by Kent Osborne's group with mouse xenografts indicates that you may need a complete blockade of the HER2 pathway in order to elicit cure. In the mouse xenografts, which are MCF-7 transfected with HER2, Osborne's group found that when they utilized a pan-HER2 blockade of trastuzumab, gefitinib and pertuzumab, tumors actually regressed completely and never came back when the combination was stopped. This is extremely exciting and I think that we're moving into an era where, unless you can block the HER family completely, you are going to provide the cell an escape mechanism.

— Jenny C Chang, MD

PRECLINICAL DATA SUPPORTING SYNERGY OF HER2-TARGETED ANTIBODIES

"Trastuzumab (herceptin) and pertuzumab (Omnitarg, 2C4) are recombinant humanized monoclonal antibodies that target different extracellular regions of the HER-2 tyrosine kinase receptor. …

"Combination drug treatment reduced levels of total and phosphorylated HER-2 protein and blocked receptor signaling through Akt but did not affect mitogen-activated protein kinase. These results suggest that combining HER-2-targeting agents may be a more effective therapeutic strategy in breast cancer rather than treating with a single HER-2 monoclonal antibody."

— Nahta R et al. Cancer Res *2004;64(7):2343-6.*