Trastuzumab Combined with Chemo/Hormonal Agents

Many of the newer, targeted biologic antitumor agents are being combined with chemotherapeutic and endocrine agents in Phase II and Phase III clinical trials, because of presumed synergy and the absence of overlapping toxicities. In the first important evaluation of this principal, a number of trials have combined trastuzumab with cytotoxic agents. Many chemotherapeutic and hormonal agents in combination with trastuzumab are currently being explored in a new generation of clinical trials. At the San Antonio Breast Cancer Symposium in December, Nicholas Robert presented encouraging initial results of a randomized trial evaluating carboplatin, paclitaxel and trastuzumab demonstrating an advantage compared to paclitaxel and trastuzumab.

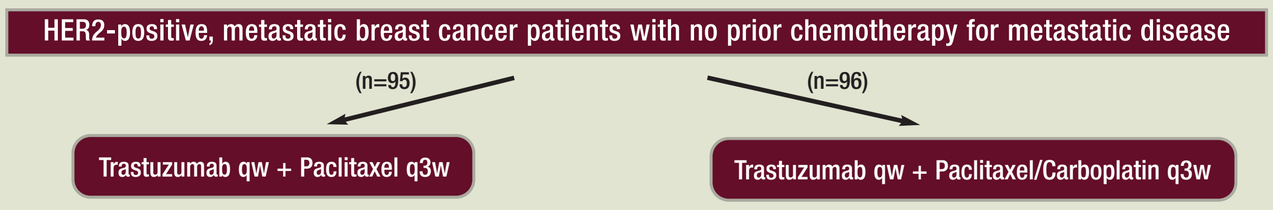
CLINICAL TRIALS OF TRASTUZUMAB COMBINATIONS IN THE METASTATIC SETTING

Protocol IDs	Target Accrual	Eligibility Criteria	Randomization Arms	
CWRU-030118, GENENTECH-H2223G, ROCHE-1100, ROCHE-B016216C, ROCHE-B016216	202	Postmenopausal, ER/PR+, HER2+ (IHC 3+ or FISH-positive) metastatic disease	Arm 1: Anastrozole qd + trastuzumab qw Arm 2: Anastrozole qd	
BCIRG-007, GENENTECH-UCLA-0109024, NCI-G02-2116, ROCHE-UCLA-0109024, UCLA-0109024	444	Stage IIIB or IV, HER2-positive breast cancer	Arm 1: [(T+C) q3w + H qw] x 8, then H q3w Arm 2: (T q3w + H qw) x 8, then H q3w	
EU-99028, SWS-SAKK-22/99	170-250	HER2-overexpressing metastatic breast cancer	Arm 1: H qw until DP, then [H qw + (paclitaxel qw x 3, followed by 1 w rest)] Arm 2: [H qw + (paclitaxel qw x 3, followed by 1 w rest)]	
CLB-9840, CTSU	580	Inoperable, recurrent or metastatic breast cancer with measurable disease and known HER2 status	**HER2 non-overexpressing** Arm 1: paclitaxel q3w Arm 2: paclitaxel qw Arm 3: paclitaxel q3w + H qw Arm 4: paclitaxel qw + H qw	**HER2 overexpressing** Arm 1: paclitaxel q3w + H qw Arm 2: paclitaxel qw + H qw
DFCI-01087, GSK-2001-P-000473/2	250	HER2+ metastatic breast cancer (IHC 3+ but FISH- are ineligible)	Arm 1: (H + vinorelbine) qw x 8 w Arm 2: H qw x 8 w + (paclitaxel qw x 8 w OR docetaxel on w 1, 2, 3, 5, 6 and 7)	

H=trastuzumab; T=docetaxel; C=cisplatin or carboplatin; DP=disease progression

SOURCE: NCI Physician Data Query, October 2002

PHASE III STUDY COMPARING TRASTUZUMAB AND PACLITAXEL WITH AND WITHOUT CARBOPLATIN IN PATIENTS WITH HER2/NEU-POSITIVE, ADVANCED BREAST CANCER



Study Results

Parameters	HTC Regimen	HT Regimen	P Value
Response Rate (RR)	48/92 52%	34/94 36%	P < 0.04
RR in HER2 IHC 3+	35/61 57%	23/63 37%	P = <0.03
Time to progression (TTP)	11.2 months	6.9 months	P = 0.007
TTP in HER2 IHC 3+	13.5 months	7.2 months	P = 0.205

HTC = trastuzumab, paclitaxel, carboplatin; HT = trastuzumab, paclitaxel

SOURCE: Robert N. Presentation, 2002 San Antonio Breast Cancer Symposium

SELECT PUBLICATIONS

Burstein HJ et al. **Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2001;19(10):2722-2730.

Ligibel JA, Winer EP. **Trastuzumab/chemotherapy combinations in metastatic breast cancer.** *Semin Oncol* 2002;29(3 Suppl 11):38-43.

Miller KD et al. **Redefining the target: Chemotherapeutics as anti-angiogenics.** *J Clin Oncol* 2001;19(4):1195-1206.

Pegram MD, O'Callaghan C. **Combining the anti-HER2 antibody trastuzumab with taxanes in breast cancer: Results and trial considerations.** *Clin Breast Cancer* 2001;2 Suppl 1:S15-9.

Robert NJ et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002;Abstract 461.

Winer EP, Burstein HJ. **New combinations with Herceptin in metastatic breast cancer.** *Oncology* 2001;61 Suppl 2:50-7.

TRASTUZUMAB PLUS CHEMOTHERAPY

For the time being, trastuzumab should not be given with an anthracycline because of potential cardiotoxicity. The standard of care is trastuzumab plus paclitaxel. Given the activity of docetaxel in women with metastatic breast cancer and the potential preclinical synergy, there are many physicians who also administer trastuzumab plus docetaxel.

Approximately three years ago, we started studying trastuzumab plus vinorelbine. In our first Phase II study with 40 women, trastuzumab plus vinorelbine was well tolerated with an overall response rate of 75%. There is an ongoing multicenter Phase III trial, with 50 sites in the United States, comparing vinorelbine/trastuzumab to a taxane/trastuzumab regimen.

—Eric P Winer, MD

RATIONALE FOR COMBINING CARBOPLATIN WITH TRASTUZUMAB/PACLITAXEL

The rationale for our Phase III trial that evaluated trastuzumab/paclitaxel with or without carboplatin in patients with HER2-positive metastatic breast cancer was really to take the pivotal trial to the next step. In the pivotal trial, trastuzumab/paclitaxel resulted in improved response rates and time to progression compared to paclitaxel alone. In the laboratory, there is preclinical synergy between the taxanes and carboplatin, and there are three clinical trials in metastatic disease, which demonstrated that the combination of paclitaxel and carboplatin produced response rates of 52%-62%. So, the next obvious step was to add carboplatin to trastuzumab/paclitaxel.

— Nicholas Robert, MD

TRASTUZUMAB SYNERGY WITH OTHER AGENTS

Systemic therapy is individualized to the patient. It depends on her prior treatment, general health, comorbid diseases and a number of other factors. All things being equal and the patient being capable, I opt for the most optimum interactive combination of carboplatin or cisplatin plus docetaxel/trastuzumab (CTH). Trastuzumab can, however, be combined with vinorelbine, capecitabine or gemcitabine.

I am quite comfortable, in a patient who cannot tolerate or does not want chemotherapy, to offer trastuzumab monotherapy. It is not, however, my usual recommendation, which is to exploit any potential synergies. HER2-positive breast cancer is very aggressive, and we want to take our best shot at the disease.

—Dennis J Slamon, MD, PhD

PHASE III TRIAL OF CTH

Platinums are active agents, and there is evidence of benefit in combining them with trastuzumab. Nicholas Robert presented an important Phase III study comparing trastuzumab and paclitaxel with and without carboplatin in patients with HER2-positive advanced breast cancer. The addition of carboplatin increased the response rate and the duration of response. I think it is important to find out whether these agents need to be combined to obtain the desired result, or whether they can be given sequentially.

— Larry Norton, MD

TRASTUZUMAB COMBINED WITH ENDOCRINE AGENTS

The HER2 and the estrogen-receptor pathways talk to one another, and coregulate one another. Preclinical data clearly demonstrate that trastuzumab can reverse tamoxifen resistance, but that question needs to be asked in the clinic. We also need to ask whether combining trastuzumab with an aromatase inhibitor might be effective, but, fulvestrant may be the most promising because it gets rid of the estrogen receptor.

— Dennis J Slamon, MD, PhD