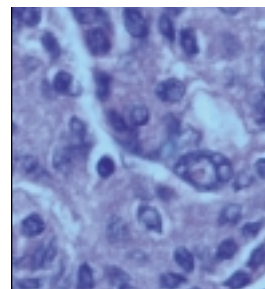


# HER2 AND TRASTUZUMAB IN BREAST CANCER

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## Introduction

The recognition and description of tumor growth control factors, together with the development of interventions that modulate their biologic activity, represent a major focus for current cancer research, which already has changed the practice of clinical oncology. These advances are proceeding rapidly, but nowhere faster than in the case of HER2 and trastuzumab.

The pace of development of new, clinically relevant information in this area can induce difficulties for clinicians in oncology to become fully aware of and quickly react to these advances. Several recent meetings have reported results that are pertinent to the field of HER2/neu and trastuzumab use in breast cancer. This article summarizes some points on HER2 testing and trastuzumab use that should be of value to treating physicians.

## Testing for HER2

The HER2 gene, also known as *c-erb* B-2 or *neu*, is one of a family of related transmembrane growth factors. Cells with increased HER2 gene copies contain an increased amount of HER2 mRNA and HER2 protein. Increased levels of the HER2 protein in tumor tissue are associated with more rapid growth of tumor cells, and patients with breast cancers that overexpress HER2 protein have a worse prognosis, measured both by relapse-free and overall survival, compared

with those who do not.<sup>1,2</sup> Besides prognostic information, some studies report that the tumor HER2 test provides evidence that there is an impaired responsiveness to tamoxifen in breast cancer patients with tumors that are both HER2 positive and hormone-receptor positive.<sup>3</sup> Others do not confirm this finding.<sup>4</sup> There is also a suggestion that chemotherapies other than cyclophosphamide, methotrexate, plus fluorouracil (CMF) may be preferred in breast cancer patients who overexpress HER2.<sup>5</sup>

The field of testing for HER2 overexpression is complicated because of a plethora of tests and antibodies that can be used, but as yet no universal standard for the tests and testing procedures exists.

Approximately one third of invasive breast cancers amplify or overexpress the HER2 gene, but controversy remains on how HER2 testing can best be utilized to predict the response of patients to treatment with trastuzumab, the humanized mouse antibody to HER2. Trastuzumab has significant antitumor properties on its own<sup>6</sup> and it prolongs survival in patients with HER2-overexpressing metastatic breast cancer when given with chemotherapy,<sup>7</sup> so identification of patients who may benefit from this intervention is important to good clinical oncology practice.

Immunohistochemical staining (IHC) is the most frequently used test to assess tumor HER2 status, since the technology to perform it is available in most pathology laboratories. IHC measures the

*No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.*

Table 1. — Treatment Effect of Trastuzumab Versus Level of IHC-Determined HER2 Expression\*

	Objective Response				
	Trastuzumab alone	Trastuzumab + paclitaxel	Paclitaxel alone	Trastuzumab + doxorubicin + cyclophosphamide	Doxorubicin + cyclophosphamide
2+ overexpression	4% (2/50)	21% (5/24)	16% (3/19)	40% (14/35)	43% (18/42)
3+ overexpression	17% (29/172)	44% (30/68)	14% (11/77)	53% (57/108)	36% (35/96)

\*The IHC test used was a research-only clinical trial assay. Herceptin® [package insert]. South San Francisco, Calif: Genentech, Inc; 2000. Adapted with permission.

expression of HER2 protein, and the FDA-approved staining kit describes a scoring system for assessment of HER2 overexpression based on cell-line controls with a known receptor density: 0 (~20,000 receptors/cell) and 1+ (~100,000 receptors/cell) are negative, 2+ (~500,000 receptors/cell) is weak positive, and 3+ (~2,000,000 receptors/cell) is strong positive. Although occasional responses to trastuzumab have been reported in patients with IHC scores,<sup>8</sup> the majority of responses occur in patients with tumors that are scored 3+ (Table 1), and most planned cooperative group studies of trastuzumab in breast cancer will select patients who have 3+ IHC results from an approved IHC test.

Problems with performance of IHC for HER2 overexpression abound, so clinicians need to be aware of the specific methodology that is used by the laboratory they use and whether the recommended methodology and scoring described in the kit (eg, the type of antibody, the antigen retrieval method used, and the reporting

system) are closely followed. IHC is less reliable in archived specimens, and thus the level of protein expression may be scored inappropriately low.<sup>2</sup> Care is also needed in interpretation by IHC of needle biopsy breast cancer specimens, since the large number of cut cells in such specimens can produce artifactually positive results. Testing for gene amplification using fluorescence in situ hybridization (FISH) technology is preferred in both of these situations.

FISH is the most commonly used test to detect HER2 DNA amplification. It is highly sensitive and specific and is suitable for use in both archived and fresh specimens. Amplification  $\geq 2$  is associated with a high proportion of responses of breast cancer to trastuzumab. Its disadvantages relate principally to laboratory time and cost issues, and it is important to ensure that infiltrating rather than in situ tumor is evaluated. Occasionally, FISH may be positive in breast tumor tissue that scores 0 by IHC.<sup>2</sup> Outcomes from using trastuzumab treatment for such patients are not known.

There was an 82% concordance between the IHC clinical trials assay (CTA) and FISH in the patients entered into the initial trastuzumab clinical trials H06489, H06499, and H06509.<sup>7</sup> No improvement in chemotherapy response rates or survival from the addition of trastuzumab occurred in FISH-negative patients entered on the initial trials of cyclophosphamide plus doxorubicin (CA) or of paclitaxel plus or minus trastuzumab. In the trastuzumab-alone studies,<sup>5,9</sup> no responses occurred in the FISH-negative group, including 17 patients who demonstrated 3+ CTA IHC scores. Thus, FISH appears to be a more precise test than IHC for determining the likelihood of a patient responding to trastuzumab.

A policy for HER testing now followed in many laboratories, including in our own institution, is for IHC testing to be performed as the standard routine test for HER2 overexpression in all newly diagnosed patients with invasive breast cancer. Test results that are reported as 3+ are accepted as being positive, and those reported as 0 or 1+ are

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considered as negative. FISH is performed routinely when IHC results are 2+ or when the 0 or 1+ IHC results are questioned from a clinical point of view, such as in a patient with a possible HER2-positive phenotype (ie, aggressive clinical course) or in old archived tissue. Most new cooperative group breast cancer protocols that study trastuzumab in breast cancer will accept patients who have either a 3+ IHC result or a positive FISH test. Some protocols require performance of both tests. It seems likely that FISH will replace IHC for assessment of tumor HER2 when automated procedures become widely available.<sup>2</sup> Measurements of circulating HER2 extracellular domain in serum are generally not used for decisions regarding trastuzumab use.

## Trastuzumab in Advanced Breast Cancer

### *Trastuzumab Alone*

Cobleigh et al<sup>10</sup> described a 15% objective response rate (CR + PR) using trastuzumab alone in 222 women with metastatic breast cancer and HER2 overexpression who had relapsed after prior chemotherapy. Subsequently, Vogel et al<sup>6</sup> reported a 26% objective response rate (95% confidence interval [CI], 18%-34%) and a 38% incidence of clinical benefit (95% CI, 29%-47%), which included patients with stable disease longer than 6 months) for trastuzumab when it was used alone as first-line therapy in 114 HER2 overexpressors. This raises the question of whether we should alter our current general policy of

almost always using trastuzumab together with chemotherapy in relatively "good-risk" patients with metastatic breast cancer, since the median time to progression for the responders in this study was an impressive 18.8 months.

### *Trastuzumab Plus Chemotherapy*

Several other trials have followed the key initial trial<sup>7</sup> (Table 1) showing that in HER2 overexpressors, trastuzumab use essentially doubled the response rate to chemotherapy with paclitaxel and with cyclophosphamide plus doxorubicin and also was associated with significantly longer survival than the chemotherapy-only treated group. High tumor response rates are reported in phase II trials that combine trastuzumab with weekly paclitaxel, with weekly vinorelbine, and with weekly paclitaxel plus carboplatin after trastuzumab induction (Table 2).<sup>11-16</sup> Combinations of trastuzumab with drugs such as docetaxel, cisplatin, gemcitabine, irinotecan, and capecitabine are planned or in progress. It is notable that the highest response rates in these studies are also in patients who are IHC 3+ or FISH overexpressors. Trastuzumab does not seem to protect against central nervous system relapse.

### *Trastuzumab Plus Hormones*

Estrogen receptor (ER) biochemistry is complex due to multiple ligand/receptor species, interactions with signal transduction pathways, and interactions with

transcriptional co-activators and co-repressors. Patients who are both ER+ and HER2 overexpressors may respond less well to tamoxifen, and the time to progression is shortened.<sup>17</sup> Combined receptor blockade with antiestrogens and trastuzumab is a rational intervention approach, and a phase II trial of tamoxifen plus trastuzumab as first-line therapy for ER+ metastatic breast cancer is in progress. A similar comparative trial including the aromatase inhibitor anastrozole and the combination of letrozole plus trastuzumab in tamoxifen-resistant HER2 and ER+ and/or PR+ breast cancer is also planned.

### *Trastuzumab Plus Novel Agents*

Ras proteins play pivotal roles in the control of normal and transformed cell growth, and at least one farnesyl transferase inhibitor, R115777, has demonstrated clinical activity in advanced breast cancer.<sup>18</sup> The opportunity to target simultaneously two crucial aspects of abnormal proliferative signal transduction is appealing, and studies combining trastuzumab with farnesyl transferase inhibitors are underway. Vascular endothelial growth factor (VEGF) supports angiogenesis, and a humanized antibody to VEGF shows antitumor activity in heavily pretreated patients with metastatic breast cancer.<sup>19</sup> There was a 9.8% response rate with 3 PRs and 1 CR at a dose level of 10 mg/kg. The combination of trastuzumab plus a VEGF antagonist is therefore also attractive for efficacy testing in clinical trials for HER2-overexpressing

breast and ovarian cancer.

The Cancer and Leukemia Group B (CALGB) has evaluated trastuzumab plus IL2 in patients with HER2 2+ and 3+ overexpressing tumors.<sup>20</sup> Two CRs and 4 PRs occurred in 33 breast cancer patients, with 3 of 6 responses at the trastuzumab dose at 4 mg/kg level and 3 of 12 at the 8 mg/kg level. A trial is now planned of low and intermediate “pulse” dose interleukin 2 in combination with trastuzumab at 4 mg/kg in breast cancer patients with measurable disease who are IHC 2+ and 3+ HER2 overexpressors who have failed treatment with trastuzumab alone.

Several biological arguments support the use of epidermal growth factor receptor (EGFR)

inhibitors to block HER2 signaling. The EGFR kinase inhibitor ZD1839 (Iressa)<sup>21</sup> inhibits HER2 phosphorylation in intact cells. Thus, the ECGR/HER2 signaling system can be targeted simultaneously at two sites: the ectodomain of HER2 with trastuzumab and the kinase pocket of the EGFR with ZD1839. This combination strategy may be more effective than trastuzumab alone in HER2-dependent breast cancers, and the concept will be tested clinically.

### Safety of Trastuzumab

The safety profile of trastuzumab has been further defined in the past year.<sup>8</sup> According to a May 2000 letter from Genentech, Inc.,<sup>22</sup>

62 serious adverse events were reported in the post-marketing setting, 15 eventuating in a fatal event that usually occurred with the first infusion. Six of the 15 who died had preexisting pulmonary compromise, and most had far-advanced disease and poor performance status. Thus, extreme caution is needed when using trastuzumab to treat patients with pulmonary compromise.

### Cardiac Dysfunction and Trastuzumab

The surprising occurrence of significant cardiac events during the initial clinical trials of trastuzumab both with and with-

Table 2. — Selected Phase II Trials Combining Trastuzumab With Chemotherapy in HER2-Overexpressing Advanced Breast Cancer

Investigator	“Line” of Therapy	Chemotherapy/Dose	Number Studied	Objective Response	Cardiac Events	Notes
Fornier et al <sup>11</sup>	1st, 2nd, or 3rd	Paclitaxel 90 mg/M <sup>2</sup> weekly	42	21/28 (71%) responses in HER2-positive patients	2 transient CHF	Heavily anthracycline-treated group
Burstein et al <sup>12</sup>	1st, 2nd, or 3rd	Vinorelbine 25 mg/M <sup>2</sup> weekly	40	24/34 (71%)	4 with grade 2 cardiac toxicity	
Burris et al <sup>13</sup>	1st	Trastuzumab induction, then paclitaxel 70 mg/M <sup>2</sup> weekly plus carboplatin AUC 2 mg/mL·min weekly; 6 doses with 2-wk rest	60 (42 evaluable)	22% ORR to trastuzumab only. ORR to HPC (16 pts) 56%; SD or better 69%	Decline in LVEF in 2 patients	8 mg/kg followed by 4 mg/kg trastuzumab dose
Kuzur et al <sup>14</sup>	1st and 2nd	Docetaxel 75 mg/M <sup>2</sup> q3w	21 (16 evaluable)	1 CR and 6 PR in 16 evaluable. 6/7 responses with IHC 3+	None	3 CNS relapses
Nicholson et al <sup>15</sup>	1st and 2nd	Docetaxel 35 mg/M <sup>2</sup> weekly	14 (34 planned)	1 CR and 6 PR in 13 assessable	Possibly 1	1 grade IV neutropenia
Malik et al <sup>16</sup>	2nd or 3rd	Docetaxel 33 mg/M <sup>2</sup> weekly	6	5 PR of 6	None	

Table 3. — Incidence and Severity of Cardiac Dysfunction in Patients Receiving Trastuzumab in Clinical Trials

	Trastuzumab alone*	Trastuzumab + paclitaxel**	Paclitaxel alone**	Trastuzumab + anthracycline + cyclophosphamide**	Anthracycline + cyclophosphamide**
Number treated	213	91	95	143	135
Any cardiac dysfunction	7%	11%	1%	28%	7%
Class III/IV	5%	4%	1%	19%	3%

\* Open-label, single-agent phase II study (94% received prior anthracyclines).  
 \*\* Randomized phase III study of chemotherapy with and without trastuzumab.  
 Herceptin® [package insert]. South San Francisco, Calif: Genentech, Inc; 2000. Adapted with permission.

out chemotherapy prompted the formation of a "Cardiac Review and Evaluation Committee" (CREC) by the manufacturer of trastuzumab. The rates of cardiac dysfunction ranged from 7% (when trastuzumab was used alone) to 11% (when used with paclitaxel in anthracycline pretreated patients) and to 28% when the drug was given concomitantly with an anthracycline in the pivotal trial (Table 3).<sup>8</sup> The majority of patients responded to standard treatment for congestive heart failure and, as of October 1999, just 3 of 314 deaths of patients in the chemotherapy trials were attributable to cardiac dysfunction. The risk factors identified for cardiac dysfunction by the CREC were prior and concomitant anthracycline administration and advanced age. Nevertheless, trastuzumab-associated cardiac dysfunction can occur in the absence of anthracycline exposure, possibly due to direct toxic effects on cardiac myocytes. The mechanism by which trastuzumab exerts its negative effects on the heart is unclear.

There is no agreement on which is the optimal method to

use to monitor cardiac function during trastuzumab treatment. Sequential measurements of ejection fraction (EF) are still the most commonly used modality, and most new trials require a baseline EF value of 50% or greater for entry. Sophisticated echocardiography is an alternate monitoring modality. Few data exist on endomyocardial biopsy. Clinical studies are being designed that will include sequential measures of circulating markers of tissue injury such as troponin T, proBNP, endothelium, and inflammatory cytokines, and they will evaluate the capability of carvedilol, a beta blocker, to prevent or minimize cardiac toxicity from trastuzumab. In clinical non-protocol practice, it would seem prudent to generally avoid trastuzumab treatment in breast cancer patients who have had  $\geq 450$  mg/M<sup>2</sup> of doxorubicin or an equivalent anthracycline dose, in those with preexisting impairment of cardiac function, and in the very old. The question of how often to monitor patients with EF during treatment remains unanswered. Clinical research protocols appropriately demand regular monitoring, but for patients who are not

being treated on a protocol who have shown no decrement in cardiac function over time, it is possible that the interval for regular EF monitoring might be lengthened in the absence of symptoms or examination findings and in the absence of a sudden cardiac stress or concomitant chemotherapy.

## Trastuzumab in Adjuvant Therapy for Breast Cancer

There is a powerful emotional and intellectual appeal to translate the survival gains from the use of trastuzumab in the advanced-disease setting to the adjuvant treatment of HER2-overexpressing breast cancer, particularly with those at greatest risk of recurrence and death. The undetermined long-term risk of cardiac problems from trastuzumab, however, demands caution, and use of the agent as adjuvant therapy is best restricted to participation in the several clinical trials that are now underway. Eligibility for these trials generally require tumors to have IHC 3+ or FISH-positive HER2 results and a pretreatment EF  $\geq 50\%$ . The Figure

summarizes the schema of several recently activated neoadjuvant and adjuvant clinical studies. All trials in the United States emphasize regular monitoring requirements for cardiac toxicity.

In Europe, a “pragmatic” trial is underway that randomizes HER2-overexpressing patients to receive trastuzumab or not after any prior

adjuvant chemotherapy for breast cancer.

## Clinical Dilemmas Regarding Trastuzumab

Many questions regarding the use of trastuzumab cannot be answered using an evidence-based approach, since the clinical experience with the antibody is too limit-

ed. The following attempts to respond to some frequently posed questions:

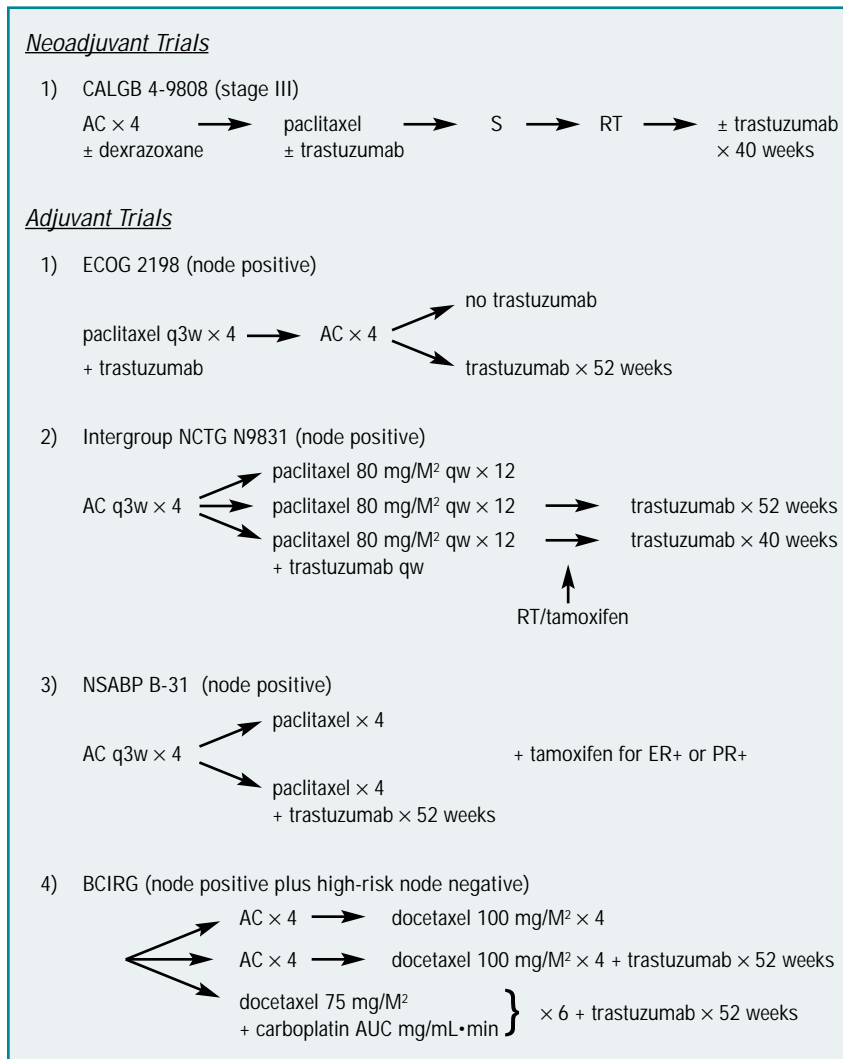
**Q:** *Should trastuzumab be prescribed to an advanced breast cancer patient with a HER2 2+ IHC result?*

**A:** As shown in Table 1, the response rate to trastuzumab alone or in combination with chemotherapy in HER2-2+-overexpressing patients is lower than in 3+-overexpressing patients. A FISH assay of this tumor should be considered prior to initiating trastuzumab therapy, since a positive result would be more effective in predicting the likelihood of a beneficial response.

**Q:** *If a patient responds and then progresses on a combination of trastuzumab plus chemotherapy, should I switch to another chemotherapy and continue the trastuzumab?*

**A:** This may be a reasonable approach if the new chemotherapy is one that has been shown to give at least additive effects with trastuzumab (eg, vinorelbine). Tripathy et al<sup>23</sup> describe that patients with metastatic breast cancer following one course of trastuzumab plus chemotherapy may respond to a subsequent course of trastuzumab-containing therapy. There are no good data, however, to support the indefinite use of trastuzumab when continued tumor progression occurs, akin to the commonly used policy of continuing androgen blockade for progressing prostate cancer.

**Q:** *Is the dose of trastuzumab of 4 mg/kg followed by 2*



Schema of selected recently activated clinical studies including trastuzumab in neoadjuvant and adjuvant therapy for breast cancer.

*mg/kg administered as a weekly intravenous infusion the best one to use?*

**A:** Yes. There is no evidence that higher doses provide more benefit. In a first-line study by Vogel et al,<sup>6</sup> the incidence of responses in HER2-overexpressing breast cancer was virtually identical in patients who received either the standard dose or double the standard dose. Studies are beginning to evaluate a more convenient schedule using an initial dose of 8 mg/kg and then 6 mg/kg every 3 weeks.

**Q:** *How long should trastuzumab alone be continued in a patient with metastatic breast cancer who is in complete remission and doing well?*

**A:** Trastuzumab should be continued probably as long as the patient is doing well and is free of cardiac toxicity. Durations of treatment lasting several years are now not uncommon. Trastuzumab does not protect against central nervous system metastasis.

## HER2 and Trastuzumab in Other Primary Sites

HER2 overexpression/ gene amplification has been described in many tumor types other than in breast cancer. Most clinical interest is currently focusing on ovarian, urothelial, and pancreas cancer and in non-small-cell lung cancer (NSCLC).

The Gynecologic Oncology Group is studying trastuzumab

alone in patients who are IHC 2+ or 3+ overexpressors and who are refractory to platinum salts and cisplatin. HER2 tends not to be overexpressed in small-cell lung cancer, but the Eastern Cooperative Oncology Group has completed a trial (ECOG 2598) that confirms the feasibility of combining trastuzumab with carboplatin plus paclitaxel in patients with IHC-overexpressing (1+ to 3+) stage IV NSCLC. Additional studies planned in the United States of HER2-overexpressing NSCLC include trastuzumab with gemcitabine plus cisplatin (M.D. Anderson Cancer Center), with docetaxel or paclitaxel given weekly (Memorial Sloan-Kettering Cancer Center), as a single agent (CALGB 9810), and with paclitaxel given weekly plus carboplatin (Southwest Oncology Group 9006). A study initiated at our institute for HER2-positive NSCLC combines trastuzumab with a triplet regimen of docetaxel, carboplatin, and gemcitabine given prior to radiation therapy for unresectable stage III disease.

## Conclusions

The recognition of the significance of the growth control factor HER2 in breast cancer and in other neoplasms has provided useful information both on prognosis and prediction of response to both hormones and chemotherapy. There is movement toward better standardization of testing methodologies for both HER2 overexpression and amplification. This will lead to better predictive measures for the use

of the growth factor antagonist trastuzumab alone or in combination with other drugs.

In patients with HER2-overexpressing breast cancer, trastuzumab exhibits major antitumor efficacy in 15%-40% and minor effects in another 20%. It has synergistic or additive interactions with several different chemotherapies and has limited acute toxicities. Cardiac dysfunction represents a significant toxicity, especially in the elderly, in those with preexisting impaired cardiovascular reserve, and in those treated with concomitant anthracyclines. The effectiveness of treatment of HER2-overexpressing advanced breast cancer with trastuzumab is leading to extensive testing of this new biologic approach in the adjuvant setting.

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