

## CORRESPONDENCE



## Trastuzumab in Breast Cancer

**TO THE EDITOR:** With regard to the reports by Piccart-Gebhart and colleagues and Romond and colleagues (Oct. 20 issue)<sup>1,2</sup> on adjuvant trastuzumab, I have two concerns. The first is that statistics based on immature data are not necessarily significant. As an example, I cite the landmark 1976 report by Bonadonna and colleagues,<sup>3</sup> which established adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) for node-positive breast cancer. They reported an extraordinary benefit in progression-free survival among postmenopausal patients at 27 months ( $P=0.001$ ). However, at 36 months,<sup>4</sup> there was less benefit ( $P=0.16$ ), and at 20 years,<sup>5</sup> there was no survival benefit from having received CMF. If Bonadonna et al. had terminated the study at 27 months, it would have been many years before a researcher would have dared to have a control group receiving no chemotherapy in a study of postmenopausal breast cancer.

The second concern is the risk of long-term cardiac effects. The dire consequences of irradiating too much of the heart in postoperative patients with breast cancer were not understood until more than 15 years after treatment. Since cardiac side effects of trastuzumab are not seen in laboratory animals, we have no long-term data.

This uncertainty should dampen our enthusiasm when prescribing adjuvant trastuzumab for patients with low-risk, HER2-positive breast cancer.

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**TO THE EDITOR:** After preoperative chemotherapy, HER2 status may change from that detected in the core biopsy specimen to that in a sample of the resected breast cancer in 4 to 35 percent of cases as assessed by immunohistochemistry and in 13 percent of cases as assessed by fluorescence in situ hybridization (FISH).<sup>1-5</sup> HER2-negative status may convert to a positive status in 2 to 9 percent<sup>1-3</sup> of patients, as assessed by immunohistochemistry or FISH, and from a positive status to a negative status in 15 to 26 percent of patients, as assessed by immunohistochemistry<sup>1,4,5</sup> or in 4 percent, as assessed by FISH.<sup>1</sup> In our limited experience, after neoadjuvant therapy with epirubicin and paclitaxel, in two of eight patients (25 percent) the HER2 status shifted to positive, and in one patient (12.5 percent) it shifted to

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negative, as assessed by immunohistochemistry. The increasing use of neoadjuvant chemotherapy and the possible introduction of trastuzumab in this setting or in adjuvant treatment raise the question of whether HER2 status should be better defined before treatment with trastuzumab is started. In the Herceptin Adjuvant (HERA) study reported by Piccart-Gebhart et al., 11 percent of those HER2-positive patients (approximately 560 patients) were treated with neoadjuvant chemotherapy; how did the authors manage the care of patients whose HER2 status changed?

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**TO THE EDITOR:** In his editorial<sup>1</sup> accompanying the reports of the results of the HERA trial and of the combined results reported by Romond et al. of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 and the North Central Cancer Treatment Group (NCCTG) trial N9831, Hortobagyi suggests that the difference in disease-free survival between the two trials can be explained by the difference in the schedule of trastuzumab administration (concurrent vs. sequential) and by the use of taxanes in only a minority of patients in the HERA trial. However, another consideration would be lead-time bias, because owing to the design of the trials, day 0 in the HERA trial was defined as after completion of adjuvant chemotherapy and a median of 8.4 months after the diagnosis of breast cancer, whereas day 0 in the North American NSABP B-31 and NCCTG N9831 trials was the day of the initiation of adjuvant chemotherapy with trastuzumab. Al-

though the authors do not provide the relevant data, day 0 in the NSABP B-31 and NCCTG N9831 trials would probably be only about four months after diagnosis. I believe that this four-month difference is enough to explain the moderate difference observed. Reanalysis of the data with a common zero point (e.g., the day of diagnosis or the day of surgery) would help to resolve this issue.

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1. Hortobagyi G. Trastuzumab in the treatment of breast cancer. *N Engl J Med* 2005;353:1734-6.

**TO THE EDITOR:** We were surprised by Hortobagyi's suggestion that the findings of Sato et al.<sup>1</sup> in their study of monoclonal antibodies against the epidermal growth factor receptor "encouraged scientists at Genentech to develop a mouse monoclonal antibody with high affinity for the extracellular domain of the HER2 transmembrane protein," since Genentech knew of more direct evidence of the therapeutic potential of antibody against Her2/neu. Beginning in the early 1980s, we collaborated with Weinberg's laboratory to develop a monoclonal antibody against Her2/neu and reported our findings in 1985 and 1988.<sup>2,3</sup> Treatment of Her2/neu-transformed cancer cells with the antibody reversed the malignant phenotype in vitro, and the antibody inhibited the growth of rodent tumors expressing Her2/neu in vivo. These observations stimulated the development by Genentech of an antibody against human Her2/neu. Genentech scientists used an immunization protocol similar to ours, and the resultant antibodies were tested similarly.

Our comments on the history of the development of Her2/neu-targeted therapeutics are in no way meant to minimize the work of the scientists at Genentech and collaborators in the development of trastuzumab (Herceptin). However, the etiquette of science dictates that the guiding published studies be recognized in a manner that maintains an accurate historical record.

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Drs. Drebin and Greene are inventors of a patent and disclosure licensed by Genentech dealing with monoclonal antibodies to p185Her2/neu.

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**TO THE EDITOR:** Remarkable advances in the treatment of breast cancer with trastuzumab were recently reported, but the use of this drug can result in substantial financial losses for the providers of the medication. Trastuzumab is sold by Genentech in 440-mg multidose vials. When a dose is prepared according to the package insert with the use of the supplied diluent, only 420 mg of trastuzumab per vial can be removed. The Centers for Medicare and Medicaid Services (CMS) sets the payment for trastuzumab on the basis of information supplied to the provider by Genentech, and the CMS assumes, on the basis of its calculations, that 440 mg can be obtained from each vial.

This difference of 5 percent is important because of the tremendous cost of trastuzumab. Each vial provides treatment for one to three patients, and each vial costs about \$2,300. The loss to the provider is about \$100 per vial. The total sales of trastuzumab in 2004 were \$483 million. The loss incurred by providers was therefore more than \$20 million. These losses will increase with expanded use of trastuzumab. The compelling nature of the results reported challenges Genentech to provide this valuable medication in a preparation that does not penalize providers.

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**DR. GELBER AND COLLEAGUES REPLY:** Dr. Gilbert expresses concern that the statistical significance observed in the trials evaluating adjuvant trastuzumab therapy for patients with HER2-positive breast cancer could be lost with additional follow-up. He cites the initial study of CMF by Bonadonna et al. as an example. The total sample size in the

trial by Bonadonna et al. was 386 patients, approximately 1/10 the size of the sample in each of the reported trastuzumab trials. The magnitude of the treatment difference observed in the HERA trial after one year of median follow-up was substantial and highly significant. Even in the unlikely case that the observation and trastuzumab groups have equivalent hazard rates beyond one year, the chance that the statistical significance would be lost after four additional years of follow-up is less than 20 percent. Nevertheless, we acknowledge that the current results reflect a reduction in the number of relapses among patients at high risk for early recurrence and that determining the ultimate magnitude of the treatment benefit for patients at risk for later recurrence, such as those with node-negative, hormone-receptor-positive disease, requires further follow-up.

We agree that the lack of information about the long-term cardiac effects of trastuzumab must be taken into account but are comforted by increasing evidence suggesting that trastuzumab-induced cardiotoxicity may be reversible.<sup>1</sup> The risk can also be minimized by optimal patient selection; in NSABP trial B-31, for instance, older patients and those who had preexisting cardiac dysfunction were at highest risk for cardiac toxic effects.<sup>2</sup> These issues should be discussed with patients, who can then make an informed decision.

Drs. Banna and Santoro cite several studies reporting that the HER2 status may change after preoperative chemotherapy. The number of patients included in these studies was small (usually fewer than 30), and all authors concluded that the observed changes in the HER2 status should be considered nonsignificant. Understandably, there is currently more concern about potential changes in the HER2 status in patients receiving preoperative trastuzumab in addition to chemotherapy. In the HERA trial, the treatment effect of trastuzumab was exactly the same for patients who received neoadjuvant chemotherapy as for those who received only postoperative chemotherapy.

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**DR. BRYANT AND COLLEAGUES REPLY:** Dr. Gilbert expresses concern that the reports on NSABP trial B-31 and NCCTG trial N9831 and the HERA trial are based on immature data. He cites as an example of the need for caution the early report by Bonadonna et al. of the statistical significance after 27 months of follow-up but not in subsequent reports. We believe that the analogy is not convincing, for several reasons. First, the preliminary report by Bonadonna et al. was based on 29 events in 209 postmenopausal patients. The results of trial B-31 and trial N9831 are based on 394 events in 3351 patients, and the HERA results are based on 347 events in 3387 patients. Both studies were reported per protocol, only after crossing prespecified reporting boundaries designed to prevent the release of premature data. The 1976 Bonadonna study was not reported in this way. The analyses in the NSABP B-31 and NCCTG N9831 trials and in the HERA trial indicated relative risk reductions for disease-free-survival events of 52 and 46 percent, respectively, with confidence intervals ruling out reductions of less than 41 to 33 percent, respectively. Data from these trials document a strong and statistically significant subsequent benefit in patients who were alive and disease-free entering their fourth year of follow-up. Bonadonna's data did not.

Although short-term cardiotoxicity data have been published, we agree with Dr. Gilbert that the long-term cardiac effects beyond three years are not yet documented and must be closely followed in the future. In this regard, continued follow-up of cardiotoxicity data is of critical importance.

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**DR. HORTOBAGYI REPLIES:** Dr. Gounaris postulates that the delay in instituting trastuzumab therapy until after the completion of chemotherapy created a lead-time bias, which could explain the differences in outcomes between the HERA trial and the combined North American trials. However, starting the disease-free survival curves four months after the initiation of adjuvant therapy in the HERA trial would have the opposite effect, leading to an artificial improvement in disease-free survival as a result of excluding patients in whom treatment failed during that interval. The remaining patients should have a better prognosis after patients with relapse are removed from the analysis.

We appreciate the perspective of Dr. Katsumata et al. on the sequence of events in the conceptual development of antibody therapy to growth factors. Their contribution to the development of monoclonal antibody therapy for HER2 was clearly important, although the concept that monoclonal antibodies have antitumor activity was already in the literature at the time of the first publication mentioned in their letter. Progress often results from consolidating knowledge from several sources; which aspect "encouraged scientists at Genentech" the most to develop trastuzumab can be determined only by those scientists.

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**DR. MASTRIANNI'S LETTER WAS REFERRED TO GENENTECH, THE MANUFACTURER OF TRASTUZUMAB, WHICH OFFERS THE FOLLOWING REPLY:** The problem with reconstituting trastuzumab (Herceptin) is not uncommon among products packaged in multidose vials. It results from compliance with the packaging regulations of the Food and Drug Administration (FDA) and government price-reporting requirements. In accordance with FDA requirements for labeling multidose vials, the vials contain 440 mg of Herceptin. The actual amount physicians obtain may differ because of

variation in the technique used to reconstitute the product with the supplied diluent and the number of withdrawals per vial.

As required by statute, the reimbursement of physicians for products administered to Medicare beneficiaries is set at 106 percent of the average sale price. Accordingly, Genentech reports its product price, which is based upon vial unit sales to

wholesalers, to the CMS on a quarterly basis. Genentech is in full compliance with all applicable FDA labeling and price-reporting requirements for Herceptin.

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## Selective Adhesion-Molecule Therapy and Inflammatory Bowel Disease

**TO THE EDITOR:** In his editorial, Podolsky (Nov. 3 issue)<sup>1</sup> suggests that monitoring with the use of magnetic resonance imaging (MRI) may be helpful in the care of patients with Crohn's disease who are receiving natalizumab therapy and are at risk for progressive multifocal leukoencephalopathy (PML). This is not an ideal approach. The long-term safety and efficacy of natalizumab are relatively unknown, and there is a lack of clarity regarding the optimal duration of treatment beyond the trial period. In an experimental model of inflammatory colitis, long-term treatment with anti- $\alpha$  integrin antibodies resulted in disease exacerbation,<sup>2</sup> indicating that the prolonged blockade of adhesion molecules is therapeutically unhelpful.

Patients with inflammatory bowel disease have an increased risk of central nervous system demyelination. There is an association of Crohn's disease with multiple sclerosis,<sup>3,4</sup> and in one study, late multiple sclerosis developed in patients with Crohn's disease despite prolonged immunosuppression.<sup>5</sup> The monitoring of patients with the use of MRI may not reliably distinguish multiple sclerosis from early PML. It is also likely that the use of other forms of immunosuppression increases the risk of PML in patients receiving natalizumab therapy.<sup>6</sup>

The future use of natalizumab should be limited to the subjects of a closely monitored research protocol. We must raise the bar of safety before approving any new treatment that targets a young population and carries a risk of death.

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**DR. PODOLSKY REPLIES:** Dr. Chaudhuri raises a number of important issues, which were touched on within the editorial. It is indeed important that any new medication be closely scrutinized before ultimate regulatory approval, and natalizumab should certainly be no exception. However, the risks of adverse effects must be kept in perspective, lest patients be deprived of all needed new therapies. With regard to the frequency of reported serious complications associated with natalizumab in patients with Crohn's disease, in the aggregate they actually appear to be less frequent than those associated with a number of approved treatments.

The presence of multiple sclerosis in patients with inflammatory bowel disease would certainly provide a potentially confounding influence, and I would agree that natalizumab, if it were approved for this indication, should not be used in the small number of patients with both conditions — in order to avoid masking the development of PML.

Finally, although the single report of a poten-