HER2 Intermediate Breast Cancers

To the Editor:

We were interested to read the article by Gilcrease et al “Even low level Her2 expression may be associated with worse outcome in node positive breast cancer” that discusses the significance of low but non-negative Her2 protein levels in the prognosis of breast cancer. As the authors note, the conventional immunohistochemical scoring system for Her2 includes cases with 1+ expression along with cases that have no staining at all in a category of negative. These patients are not thought to be candidates for Her2-targeted therapy. The authors compare 53 Her2 0 cases and 13 Her2 1+ cases (66 total), and find a significantly worse outcome in patients with low level Her2 protein expression.

We too have looked at the significance of low HER2 levels. In our 2008 study “New cut-points to identify HER2 copy number: analysis of a large population-based cohort with long-term follow-up,” we looked at 1023 cases with HER2 fluorescent in situ hybridization (FISH) and HER2 immunostaining results with 2 different anti-HER2 antibodies. We determined that a group of cases with an intermediate HER2 amplification ratio range of 1.5 to 2.2 have a significantly better outcome than cases positive for amplification by conventional criteria (amplification ratio > 2.2) and a significantly worse outcome than cases with an amplification ratio less than 1.5. This group of intermediate HER2 amplified cases represented 13% of the total cohort suggesting that this is a clinically important group to recognize.

The article by Gilcrease et al prompted us to revisit our data and examine whether we find similar results with immunohistochemistry alone. In contrast to the findings of Gilcrease et al, our study with a similar cohort (node positive cases that were treated with a partial or complete mastectomy, chemotherapy, and radiation therapy) with 2 different HER2 antibodies (A0485 and 4B5) scored independently by 2 teams of surgical pathologist (R.B.W. with K.C.J and T.O.N. with C.B.G.) failed to demonstrate a significant difference in outcome between 0 and 1+ cases (sample size of cases that were 0 and 1+ was 161 and 143, respectively).

Although it is possible that Gilcrease et al have identified a significant group of HER2 intermediate cases, the method used (detection of low level protein expression by immunohistochemistry) is subject to variability such that the same conclusions are not realized in our study. As such, we believe it cannot be applied in practice. Although they indirectly corroborate our 2008 study, it may be that the quantitative nature of the FISH assay has advantages when trying to make subtle distinctions in HER2 status.

The 2007 guidelines supported by College of American Pathologists and American Society of Clinical Oncology have contributed greatly needed organization to HER2 testing and reporting. We recognize that modifications should be made to this with great caution. However our study on HER2 FISH ratios and this more recent study by Gilcrease et al on HER2 protein expression, combined with the findings presented at a recent meeting suggests that changes to these guidelines will have to be made in the future.

It has yet to be proven that HER2 intermediate breast cancers respond to targeted anti-HER2 therapy. In light of the above suggested findings, it might be more appropriate to phrase this as “respond greater than HER2 negative breast cancers.” But our studies and those by Gilcrease et al show that HER2 levels at an intermediate range influence breast cancer behavior and there may be a favorable response to HER2 targeted therapy. Ultimately, both immunohistochemistry and FISH should be used when the important question of prediction of responsiveness to Herceptin therapy is addressed, as it is not clear which is best at this point.

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REFERENCES

In Response:

On behalf of my co-authors, I would like to thank Jensen et al for their interest in our paper, which prompted them to reevaluate the data in their 2008 study. Although they did not observe a worse outcome for patients with 1+ HER2 protein expression compared to patients with a score of 0, it is important to note that there are some potentially significant differences between their study and ours.

The number of patients included in our study was small because we...