Determining True HER2 Gene Status in Breast Cancers With Polysomy by Using Alternative Chromosome 17 Reference Genes: Implications for Anti-HER2 Targeted Therapy

Chun Hing Tse, Harry C. Hwang, Lynn C. Goldstein, Patricia L. Kandalaft, Jesse C. Wiley, Steven J. Kussick, and Allen M. Gown

ABSTRACT

Purpose
The ratio of human epidermal growth factor receptor 2 (HER2) to CEP17 by fluorescent in situ hybridization (FISH) with the centromeric probe CEP17 is used to determine HER2 gene status in breast cancer. Increases in CEP17 copy number have been interpreted as representing polysomy 17. However, pangenomic studies have demonstrated that polysomy 17 is rare. This study tests the hypothesis that the use of alternative chromosome 17 reference genes might more accurately assess true HER2 gene status.

Patients and Methods
In all, 171 patients with breast cancer who had HER2 FISH that had increased mean CEP17 copy numbers (> 2.6) were selected for additional chromosome 17 studies that used probes for Smith-Magenis syndrome (SMS), retinoic acid receptor alpha (RARA), and tumor protein p53 (TP53) genes. A eusomic copy number exhibited in one or more of these loci was used to calculate a revised HER2-to-chromosome-17 ratio by using the eusomic gene locus as the reference.

Results
Of 132 cases classified as nonamplified on the basis of their HER2:CEP17 ratios, 58 (43.9%) were scored as amplified by using alternative chromosome 17 reference gene probes, and 13 (92.9%) of 14 cases scored as equivocal were reclassified as amplified. Among the cases with mean HER2 copy number of 4 to 6, 41 (47.7%) of 86 had their HER2 gene status upgraded from nonamplified to amplified, and four (4.7%) of 86 were upgraded from equivocal to amplified.

Conclusion
Our results support the findings of recent pangenomic studies that true polysomy 17 is uncommon. Additional FISH studies that use probes to the SMS, RARA, and TP53 genes are an effective way to determine the true HER2 amplification status in patients with polysomy 17 and they have important potential implications for guiding HER2-targeted therapy in breast cancer.

J Clin Oncol 29:4168-4174. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Amplification of the human epidermal growth factor receptor 2 (HER2) gene and attendant protein overexpression are present in 10% to 20% of primary breast cancers.1-3 HER2 overexpression and/or gene amplification is a negative overall prognostic marker,4 as confirmed in gene array studies.5,6 HER2 status also predicts sensitivity to anthracycline-based chemotherapy regimens7-10 as well as relative resistance to cyclophosphamide-based regimens11 and tamoxifen-based therapies in the setting of estrogen receptor–positive breast cancers.12 Most importantly, breast cancers with HER2 alterations are now treated with targeted therapies such as trastuzumab and lapatinib, which have been shown to markedly improve response rate and survival when added to chemotherapy or as monotherapy.13-20

HER2 testing has become an essential part of the clinical evaluation of all patients with breast cancer, and accurate HER2 results are critical in identifying appropriate patients for targeted therapies. In 2007, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) released guidelines for laboratory testing of HER2 status in breast cancer.21,22 The goal of these guidelines was to ensure maximal accuracy of HER2 testing by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). However, these