From the Editor

Personalized Therapy Requires Rigor in Biomarker Performance

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Personalized medicine is all about tailoring therapy based on clinical and biomarker characteristics, allowing us to derive the most focused benefit/risk ratio. Early successes in personalized medicine were seen as early as the 1960s as cytogenetics provided a basis for classifying leukemias, the identification of estrogen receptors in some breast cancers, and in the mid-1980s, the demonstration that amplification and overexpression of the *HER2* gene that encoded a growth factor receptor was associated with a worse outcome.[1] This culminated in early trials showing that the humanized anti-HER2 antibody trastuzumab was effective against *HER2*-overexpressing breast cancer.[2,3]

This issue of *The American Journal of Hematology/Oncology®*, Dr Press and colleagues affirm that when it comes to biomarkers, the devil is in the details. Nearly 20 years after the approval of trastuzumab, there remains controversy and shifting criteria for the use of fluorescence in situ hybridization (FISH) to define *HER2* amplification status and on this basis to recommend HER2-targeted therapy, which impacts survival in early and advanced breast cancer. Although the genome guides the expression of proteins, it is proteins that ultimately drive biology. In the case of the estrogen receptor, protein expression is mediated by transcriptional control and not gene copy number. In the case of *HER2*, it is mostly the opposite case–protein expression levels are guided by gene copy number. However, a confounding factor is that amplifications tend to involve large segments of, or even, the entire chromosomes. Probes must be large enough to be visible, so it is necessary for them to span several genes. It is also necessary to normalize gene copy number to chromosome copy number, typically assessed by probing the chromosome centromere (CEP), over an area that also encompasses several genes. The relationship between gene copy number and expression varies not only for specific genes, but possibly among cases for a given gene, so it is critical to develop a robust body of data to formulate a reliable assay.

In this article, actual observed outcomes on the basis of assay results with the targeted therapy in question, the ultimate proof for the utility of biomarkers and their thresholds for positivity, are provided for the categories of controversy that include the "equivocal" category for gene amplification based on FISH assays. Because the *HER2*/CEP17 ratio (≥ 2.0 for positivity) was used for the basis of the trials described in this article, it was possible to describe the outcomes of the equivocal group, representing nearly 5% of all cases. Please read this important article for the punchline—it may influence your opinion on the ongoing controversy regarding the guidelines for interpreting *HER2* results—the underpinning for the use of HER2-targeted therapy and its clear clinical benefits.

References

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177-182.
2. Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *J Clin Oncol.* 1996;14(3):737-744.
3. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783-792.