otherwise met criteria for trial N9831. However, in a separate article describing a HER2 testing round robin study, Dr Perez et al. (6) reported that, despite excellent concordance, the overall discordance for IHC and FISH testing among international experts were 4% and 3%, respectively, which exceeds the 1% reported in the current analysis (1). Those data highlight persistent issues of assay interpretation, tumor heterogeneity, and platform robustness, even among experts in the field, which continue to challenge HER2 testing in daily practice.

Nonetheless, it is reassuring that the concordance between local testing in laboratories throughout the United States and confirmatory central HER2 testing at the Mayo Clinic (Rochester, MN) for the recently completed Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation HER2 adjuvant trial showed that only approximately 5.8% of patients initially deemed eligible were not centrally confirmed to be HER2 positive (7). This is substantially lower than the cumulative HER2 false-positive rates ultimately reported for trial N9831 of 18% (IHC) and 12% (FISH) (8). These results suggest progress in standardizing HER2 testing, in part, because of greater attention to preanalytic and analytic factors, which we believe results from the implementation of routine proficiency testing since early 2007, and reinforce the potential critical value of ongoing efforts by organizations like ASCO and CAP and the practical benefit of providing access to high-quality predictive biomarker testing to all patients everywhere. Nonetheless, the issue of equivocal test results will be carefully considered in a planned upcoming update of the HER2 Testing Guideline along with evidence on the current frequency of this occurrence following guideline implementation.

Response

We are appreciative of having received this correspondence and the opportunity to reply. We stand by our numerical assessments as well as recommendations for using the originally used US Food and Drug Administration (FDA) criteria for definition of HER2 positivity for decision making related to anti-HER2 therapy.

One of the critical issues that we would like to avoid is not offering anti-HER2 therapy to patients whose tumors are HER2 positive based on data from clinical trials reported to date. We agree that performing the alternative HER2 test if the tumor assessment is considered “equivocal” by American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) joint guidelines may indeed diminish the number of patients whose tumors are truly HER2 positive but do not meet the definition of positivity by the 2007 ASCO/CAP guidelines. However, this extra testing adds expense to the health-care system and does not improve predictability of benefit of adjuvant anti-HER2 therapy. The correspondence from Wolff et al. quotes a preliminary high-level summary of HER2 testing in ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimization), but we advise against presuming that these will be the ultimate findings after full analysis of the ALTTO HER2 central testing. Finally, the information of our HER2 Round Robin project (comparison amongst three expert pathology groups using a subset of previously centrally tested specimens from the three large adjuvant trials N9831, BCIRG005, and BCIRG006) (1) should be used with caution in the context of applying the results to pathologists not involved in central HER2 testing as part of clinical trials.

In closing, we are fully supportive of raising the level of visibility related to HER2 testing issues including issues related to techniques and methods, and data interpretation that directly affect patient care. We are collaborating on an ongoing meta-analysis of the trastuzumab adjuvant clinical trials that will provide an additional opportunity to investigate the benefit of trastuzumab in the albeit small but important subgroup of patients whose disease falls in the window between the FDA and...
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Reference

Notes
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