Re: Predictability of Adjuvant Trastuzumab Benefit in N9831 Patients Using the ASCO/CAP HER2-Positivity Criteria

In a retrospective analysis of the adjuvant trastuzumab trial N9831 recently published in the Journal, Perez et al. (1) compared the frequency of HER2-positive status as was determined by the US Food and Drug Administration (FDA) criteria for eligibility for the trial with post hoc criteria proposed by the 2007 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) HER2 Testing Panel (2). They concluded that the FDA, rather than ASCO/CAP criteria should be used to determine the eligibility of breast cancer patients for trastuzumab adjuvant therapy. Indeed, this recommendation is not dissimilar from the original recommendations of the ASCO/CAP HER2 Testing Panel (3,4). The Panel recommended that “equivocal” categories be established for HER2 that were meant to trigger HER2 reflex testing using another appropriately validated assay platform such as fluorescent in situ hybridization (FISH) if immunohistochemical (IHC) staining for HER2 was equivocal or with IHC if FISH results were equivocal. In this regard, the ASCO/CAP Panel recommended that the percentage of cells with strong uniform membrane staining by IHC required to deem a case 3+ be increased from the 10% used in the FDA eligibility requirements to 30% and that 11%-29% should be considered equivocal and trigger confirmatory FISH testing. The Panel also recommended routine proficiency testing, which has since been widely adopted by the pathology community as shown by the uptake since the year 2007 in the numbers of labs in the United States and elsewhere participating in predictive marker proficiency testing as part of the College of American Pathologists Laboratory Improvement Program (Figure 1) (5). Overall, the Panel felt that this strategy would provide clinicians and patients with additional confidence as eligibility for adjuvant trastuzumab was determined (4).

However, in their report, Perez et al. state that on the basis of their retrospective assessment of the N9831 trial, “up to approximately 4% of patients may miss receiving a recommendation to receive adjuvant trastuzumab, depending on the testing done, if the ASCO/CAP vs the FDA cutoffs for HER2 positivity are used” (1). Although we agree that undertreatment of patients with trastuzumab is problematic, we do not feel this estimate is accurate. A 4% undertreatment would only occur if the HER2 guideline recommendations for reflex testing are ignored. Indeed, Perez et al. state that “determining HER2 positivity on the basis of both IHC and FISH results vs either IHC or FISH alone decreases the number of ineligible patients and decreases the number of false-negative results.” To be more specific, 107 patients in N9831 had tumors for which more than 10%-30% of cells had 3+ membrane staining by IHC (1). These patients were eligible by FDA criteria for N9831 but would now be considered equivocal per ASCO/CAP criteria. Of the 100 patients then also tested by FISH, 78 had a FISH HER2/CEP17 ratio of more than 2.2 and would have been deemed HER2 positive by ASCO/CAP criteria. Thus, the remaining 22 patients (22% of the 100 IHC equivocal patients, but 0.78% of the entire 2809 patients with dual testing in N9831) would be considered HER2 negative by ASCO/CAP criteria. Conversely, if FISH were the primary test, 37 patients had equivocal ASCO/CAP criteria ratios of 2.0 to 2.2. When tested by IHC, six (16%) would have been IHC 3+ with greater than 30% strong membrane staining and confirmed HER2 positive by ASCO/CAP criteria, whereas 31 (84%) of the 38 patients with dual testing) had tumors that had ASCO/CAP equivocal IHC 3+ staining in more than 10% but less than 30% of cells and would thus be considered HER2 negative. Assuming a HER2 overexpression frequency of 15% in the general population of newly diagnosed breast cancer patients, we estimate that approximately 0.15% of all patients would fall into the category of undertreatment using ASCO/CAP guidelines compared with FDA trial eligibility criteria.

Given the remarkable reduction in recurrence and mortality offered by adjuvant trastuzumab, the ASCO/CAP HER2 Panel does not take lightly that its criteria might have led to undertreatment of up to 1.1% of patients with HER2-positive tumors that...
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 Optimization 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 pre-analytic 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.

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References

Notes
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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) (I) 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