

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-84.

Immunohistochemical tests for HER2 and tests for overexpression of *HER2* by FISH.

Central laboratory testing of HER2 expression and amplification of tumor specimens from the first 104 B-31 patients was discordant with results submitted by the participating institutions in 18% of cases. Discordance was more likely when the initial assay was done by immunohistochemistry in laboratories that performed fewer than 100 assays per month.¹ The B-31 protocol was therefore amended to require that HER2 determinations be made by immunohistochemistry at NSABP-approved reference laboratories or by FISH. Thereafter, there was 97% concordance between the initial HER2 determinations and confirmatory FISH assays at the NSABP Pathology Section.²

Before January 11, 2002, institutions participating in N9831 registered patients based on local HER2 testing. However, because of poor concordance between local and central HER2 testing,³ patients could be registered based on local HER2 testing, but after January 11, 2002, they were not informed of their treatment assignment until central testing confirmed results of FISH or immunohistochemistry.

Statistical Notes

The intention-to-treat analysis includes all patients who refused protocol therapy for whom follow-up is available. After 1/11/2002, N9831 patients were randomized conditionally on central confirmation of HER2-positivity. N9831 patients found to be HER2-negative on central testing following this amendment are excluded from the analyzed cohort. Exclusion of these patients is consistent with the intent-to-treat principle, since the pathologic specimens required for blinded central testing were obtained prior to randomization.

One B-31 patient was confirmed to have metastatic disease based on conclusive findings dated prior to randomization. This patient was not at risk for the primary endpoint and was excluded.

Definitions of endpoints

Time to recurrence was defined as the time from randomization to first locoregional or distant treatment failure, ignoring any intervening contralateral breast cancers or other second primary cancers. Deaths without evidence of recurrence were treated as censoring events. Time to distant recurrence was defined to be the time from randomization to first distant metastasis, ignoring any intervening locoregional failures, contralateral breast cancers or other second primary cancers.

References

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2. Paik S, Tan-Chiu E, Bryant J, Romond E, Brown, A, Mull J, et al. Successful quality assurance program for HER2 testing in the NSABP Trial for Herceptin. *San Antonio Breast Cancer Symposium*, 2002;9 (abstr)
3. Roche PC, Suman VJ, Jenkins RB, Davidson NE, Martino S, Kaufman PA, et al.. Concordance between local and central laboratory HER2 testing in the Breast Intergroup Trial N9831. *J Natl Cancer Inst* 2002;94:855-7.







