Controversies in HER2 and Estrogen Receptor Testing

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San Antonio Breast Cancer Symposium 2

Systemic treatment of breast cancer has become an oncologic model for the use of tissue predictors of tumor response. Specifically, clinicians routinely utilize estrogen and progesterone receptor assays in considering endocrine treatment and HER2 testing when trastuzumab is an option. Estrogen receptor results may also predict response to chemotherapy, and HER2 testing may correlate with response to specific cytotoxic agents. The clinical importance of these two tissue analyses in both clinical research and practice is complicated by inconsistencies in performance and interpretation of these assays. Recent quality control reports on HER2 testing from the NSABP and Intergroup trials have led to concerns about community-based testing. Dr Craig Allred's work on inconsistent quality control of ER testing in the community has also raised concerns that selection of patients for endocrine therapy may be suboptimal.

NSABP-B-24 DATA: CLINICAL COMPARISON OF ER-NEGATIVE RESULTS FROM OUTSIDE AND CENTRAL LABS

		Events/patients (%)			
Lab	n	Placebo	Tamoxifen	Relative risk	*p*-value
Outside lab ER-negative results	64	10/39 (26%)	3/25 (12%)	0.43 (↓57%)	0.20
Central lab ER-negative results	89	11/48 (23%)	11/41 (27%)	0.99 (↓1%)	0.98

SOURCE: Allred DC. **ER status and response to tamoxifen in ductal carcinoma in situ (DCIS).** Presentation. San Antonio Breast Cancer Symposium, 2002.

ALLRED SCORE FOR ER STATUS (0-8)*

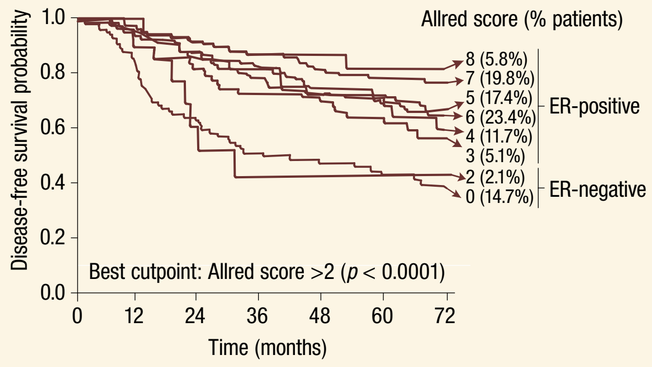
% staining score	Proportion of positive staining cells	Intensity score	Average intensity of positively stained cells
0	none	0	none
1	<1/100	1	weak
2	1/100 to 1/10	2	intermediate
3	1/10 to 1/3	3	strong
4	1/3 to 2/3		
5	>2/3		

* Allred Score = percent staining score + intensity score

DERIVED FROM: Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81.

ALLRED SCORING OF ER STATUS BY IHC PREDICTS RESPONSE TO ADJUVANT ENDOCRINE THERAPY

Patients receiving any endocrine therapy (n=777)



DERIVED WITH PERMISSION FROM: Harvey JM et al. *J Clin Oncol* 1999;17(5):1474-81.

DETERMINATION OF ESTROGEN RECEPTOR STATUS BY MEDICAL ONCOLOGISTS

How do you define ER positivity?	
Any staining	24%
Staining above lab cutoff	70%
Staining above individual cutoff value you determine	6%
Do you request ER status for ductal carcinoma *in situ*?	
Yes	58%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

COMPARISON OF LOCAL AND CENTRAL HER2 TESTING IN NCCTG-N9831 AND NSABP-B-31

Study	Local testing IHC 3+ confirmed by central HercepTest®	Local testing IHC 3+ HER2 gene amplification exhibited in central testing
NCCTG-N9831 (n=119)[1]	74%	66%
NSABP-B-31 (n=104)[2]	79%	79%

SOURCES: [1] Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7.
[2] Paik S et al. *J Natl Cancer Inst* 2002;94(11):852-4.

HER2 STATUS FOLLOWING PREOPERATIVE TRASTUZUMAB AND PACLITAXEL

	Baseline HER2 status			
	3+ (n=32)		2+ (n=8)	
HER2 status after preoperative therapy	No. of patients	%	No. of patients	%
3+	17	53	1	13
2+	2	6	0	0
1+ or 0	4	13	3	37
Not assessable	3	9	3	37
Pathologic complete response	6	19	1	13

SOURCE: Burstein HJ et al. *J Clin Oncol* 2003;21(1):46-53.

FALSE-POSITIVE RATES FOR HER2 TESTS PERFORMED BY NSABP-APPROVED LABORATORIES

Original assay used by NSABP-approved laboratory	Central PathVysion® FISH assay not amplified
FISH (n=133)	4.5%
IHC (n=107)	2%
Total (n=240)	3%

SOURCE: Paik S. Presentation, San Antonio Breast Cancer Symposium, 2002. **Successful Quality Assurance Program for HER2 Testing in the NSABP Trial for Herceptin®.** *Breast Cancer Res Treat* 2002;76(Suppl 1);Abstract 9.

SELECT PUBLICATIONS

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;76(Suppl 1);Abstract 30.

Allred DC et al. **Prognostic and predictive factors in breast cancer by immunohistochemical analysis.** *Mod Pathol* 1998;11(2):155-68.

Burstein HJ et al. **Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing Stage II or III breast cancer: A pilot study.** *J Clin Oncol* 2003;21(1):46-53.

Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81.

Paik S et al. **Real world performance of HER2 testing – National Surgical Adjuvant Breast and Bowel Project Experience.** *J Natl Cancer Inst* 2002;94(11):852-4.

Press MF et al. **Comparison of HER-2/neu status determined by fluorescence in situ hybridization (FISH) in the BCIRG central laboratories with HER-2/neu status determined by immunohisto-chemistry or FISH in outside laboratories.** Poster. SABCS, 2002;Abstract 238.

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the Breast Intergroup Trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7.

Taucher S et al. **Do we need HER-2/neu testing for all patients with primary breast carcinoma?** *Cancer* 2003;98(12):2547-53.

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DEFINING ER POSITIVITY

Assessment of ER status remains problematic. While the IHC method can be performed in any pathology laboratory, in some the quality control is poor. The real problem with false-negative results occurs for tumors with low levels of ER — between one and 20 percent of positively staining cells — which comprises 10 percent of patients. These patients will be labeled ER-negative and will not receive the benefit of endocrine therapy.

— Anthony Howell, MD

DEFINING ER STATUS

We are in an era in which every pathology laboratory should report the percentage of tumor cells staining positive for estrogen receptors, rather than just reporting "positive" or "negative." Negative should be defined as tumors with virtually no cells staining positively — truly "stone cold zero." Data show that women whose tumors with just a few percent of cells expressing estrogen receptors derive benefit from endocrine therapy. A common standard in the United States is for laboratories to report a specimen with less than 10 percent of tumor cells staining as being negative. When invasive breast cancer is reported to be ER-negative, you should call your pathologist and verify the numbers. It's not just academic any more; it's very important in treating patients.

— Hyman B Muss, MD

ASSESSMENT OF ER STATUS IN PATIENTS WITH DCIS

In the original NSABP-B-24 study, which randomly assigned women with DCIS to adjuvant tamoxifen or placebo, ER status was not measured. Craig Allred and the NSABP subsequently retrieved 600 to 800 blocks from that trial and found that ER status strongly influenced the benefit from tamoxifen, whereas in patients with ER-negative disease, the recurrence rates were almost identical and the small, nonsignificant benefit seen was probably related to quality control of the ER assay. Quality control in determining estrogen receptor status is an important issue. Grade I DCIS is almost always positive; if it's reported as ER-negative, one should question the accuracy of the assay.

— Seema A Khan, MD

LOCAL VERSUS CENTRAL HER2 TESTING

We were surprised when we found poor concordance between community and central laboratory HER2 testing, in terms of both HER2 protein expression and gene amplification. The data from the first 119 cases were so important that we actually changed the eligibility criteria for this trial (NCCTG-N9831). Physicians can still conduct local HER2 testing, but we test the tumor specimens again by the HercepTest® and the PathVysion® FISH assay. If neither demonstrates HER2 positivity, we send the specimen to another central laboratory and if that laboratory also finds that the tumor is HER2-negative by both assays, then we notify the physician that the patient should not participate in the trial.

— Edith A Perez, MD

INFLUENCE OF TRASTUZUMAB ON HER2 STATUS

We don't know what happens to a patient's HER2 status after they have been treated with trastuzumab. In the metastatic setting, some case series of pre- and post-treatment biopsies have reported conflicting results. Because most of the trastuzumab trials have been conducted in patients with metastatic disease, in whom it is difficult to obtain biopsies, no good database of pre- and post-treatment tumor tissues exists.

HER2 gene amplification appears to be very stable. Several studies have shown good concordance between the HER2 status in the primary tumor and the metastases. Given that level of concordance and the presumed genetic stability for HER2 amplification, I would be very surprised if trastuzumab could change HER2 gene amplification. I suspect that if one rebiopsied residual tumor after trastuzumab therapy, one would find the HER2 gene still amplified. It's just mind-boggling that we haven't done that yet. We need to do a better job of obtaining tissue for laboratory analysis.

— Mark D Pegram, MD