

# EVIDENCE WATCH

## A review and assessment of recent clinical trial data

*Oncology Exchange* provides overviews of important clinical trial data originally presented at the 27<sup>th</sup> San Antonio Breast Cancer Symposium (SABCS), December 8–11, 2004. Leading Canadian experts offer commentary and clinical interpretations.

### Breast cancer

#### REPRODUCIBILITY OF SEVERAL GENE EXPRESSION SIGNATURES IN PREDICTING OUTCOME IN BREAST CANCER.

**Investigators:** D.S.A. Nuyten et al.

This was a reexamination of 295 Stage 1–2 breast cancer cases previously evaluated with a 70-gene “prognosis profile” that predicts risk for metastases. Gene expression data of 25,000 genes were obtained using microarray analysis and 2 new techniques: a classification using the Intrinsic Gene Set into tumour types:

basal, luminal A, luminal B, HER2 and normal epithelium-like tumours; and a “Wound Signature” gene expression pattern shown in a previous series to predict poor outcome in patients with tumours positive for the Wound Signature (WS+). The 169 patients with quiescent or WS– tumours had a 75% probability of being

metastasis-free at 10 years, compared to a 50% probability in the 126 patients with activated or WS+ tumours ( $p < 0.00001$ ). Probabilities of overall survival (OS) were 85% and 51%, respectively ( $p < 0.00001$ ). As shown in **Table 1**, the tumour classifications also differentiated patient subgroups as to prognosis.

#### EXPRESSION OF THE 21 GENES IN THE RECURRENCE SCORE ASSAY AND PREDICTION OF CLINICAL BENEFIT FROM TAMOXIFEN IN NSABP STUDY B-14 AND CHEMOTHERAPY IN NSABP STUDY B-20.

**Investigators:** S. Paik et al.

The 21-gene Oncotype DX™ Recurrence Score (RS) assay was previously found, in a retrospective analysis of the tamoxifen-only arms of the NSABP B-14 and NSABP B-20 studies, to predict distant recurrences in patients with node-negative, estrogen receptor-positive (ER+) breast cancer treated with tamoxifen alone. This updated followup evaluated the RS’s ability to predict tamoxifen and chemotherapy benefit. In 355 patients from NSABP B-14, those

with high quantitative ER score had greater benefit with tamoxifen, and they usually also had low RS. Those with low quantitative ER, who also generally had high RS, had less benefit with tamoxifen. The interactions between both tamoxifen treatment and high quantitative ER and between tamoxifen treatment and RS were statistically significant ( $p < 0.05$ ). Patients in NSABP B-20 ( $n = 434$ ) whose tumours had  $RS \geq 31$  obtained the greatest benefit from

chemotherapy, with an absolute increase in 10-year distant recurrence-free survival of  $27.6 \pm 8.0\%$  (mean  $\pm$  SE). Those with  $RS < 18$  derived little or no benefit from chemotherapy, with an absolute decrease in 10-year distant recurrence-free survival of  $1.1 \pm 2.2\%$  ( $p < 0.05$ ). Thus, the authors conclude, the assay both quantifies the likelihood of disease recurrence and predicts the chemotherapy benefit expected in women with node-negative, ER+ breast cancer.

**COMMENTARY:** Joseph Ragaz, MD, FRCPC, Director, Oncology Program, McGill University Health Centre, Montréal, QC.

Seldom in the history of cancer research has there been so much excitement as with the development of new techniques

involving complementary DNA (cDNA) and tissue microarrays. These techniques involve photolabelled

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hybridized RNA probes that enable visual display of upregulated or downregulated tumour genes and their controls. The 2004 SABCs dedicated a large segment of the program to the genetic classification of human breast carcinoma using cDNA techniques. Martin Piccart presented an extension of the originally reported studies of the “tumour signature” concept in node-negative untreated breast cancer, confirming that the Amsterdam 70-gene prognostic signature outperformed both the NIH and the St. Gallen criteria in predicting recurrences and overall survival.<sup>1</sup> Two studies presented by Dmitry Nuyten of the Netherlands Cancer Institute in Amsterdam and Soonmyung Paik of South Korea are discussed here.

**TABLE 1. Outcome according to WS vs 70-gene signature subtypes**

WS status (no. of patients)	Disease-free survival	Overall survival
WS- (n = 169)	75%	84%
WS+ (n = 126)	50%	51%
70-gene signature categories (% of patients)		
70-gene signature categories (% of patients)	Disease-free survival	Overall survival
basal type (16%)	52%	45%
HER2 (17%)	55%	55%
luminal B (27%)	60%	70%
luminal A (29%)	76%	86%
normal epithelium-like (11%)	78%	87%

**Wound Response Signature**

The WS is a new entity derived from the characterization of upregulated genes involved with the healing of post-mastectomy wounds or other areas of body trauma followed by healing. These genes govern collagen and fibrous tissue formation and are associated with a complex interaction of mastocytes, lymphocytes and other vectors of human immunity. WS identified 126 tumours as positive or activated and 169 as negative or quiescent. **Table 1** shows that the simple 2-group categorization of WS — positive vs negative — significantly discriminated both DFS and OS, comparing favourably with the 5-category classifications of the 70-gene signature. While the 2 extreme groups of the latter (the basal and the “normal-like”) discriminated high from low risk satisfactorily, with a similar relative risk magnitude as the WS, only 27% of patients’ tumours fell into these categories. The remaining majority were subdivided into the 3 remaining categories of the 70-gene signature, and showed much less outcome variation. Multivariate survival analysis showed WS to be a significant predictor for both death rate and recurrences (OS, HR = 3.7; 95% CI 1.53–9.21, p = 0.006; DFS, p < 0.00001) — more accurate than tumour grade, nodal status, receptor status and the 70-gene signature. These data validate the prognostic capacity of the WS, and confirm the authors’ hypothesis that combining the 70-gene prognostic profile with WS improves risk stratification.

**Recurrence Score assay**

The Oncotype DX™ 21-gene Recurrence Score assay is designed to yield a recurrence score (RS) based on a panel of 16 cancer genes and 5 reference genes that enables clinicians to categorize patients as being at low, intermediate or high risk for recurrence. In the NSABP B-14 Tamoxifen Benefit Study, 645 patients with node-negative, ER+ breast cancer were randomized to receive either tamoxifen or placebo.<sup>2</sup> Tamoxifen significantly increased the distant recurrence-free survival (DRFS), the primary endpoint, in patients deemed at intermediate risk for recurrence by the assay. Patients identified as high risk for recurrence by the RS assay, however, did not benefit from tamoxifen. In the NSABP B-20 Chemotherapy Benefit Study, 651 patients with node-negative, ER+ breast cancer were randomized to receive tamoxifen alone or tamoxifen plus either methotrexate and 5-fluorouracil (5-FU) or cyclophosphamide, methotrexate and 5-FU.<sup>3</sup> The main study endpoint was also DRFS. Paik et al reported here that the Oncotype RS assay accurately predicted response to chemotherapy: the addition of chemotherapy to tamoxifen in the assay’s high-risk category of patients reduced the risk of distant recurrence at 10 years from 88% to 60% (p = 0.001), while patients categorized as low risk did not benefit from the additional chemotherapy. This study documented that genetic signatures have both prognostic value, identifying high-risk and low-risk cases, and also have predictive value in confirming who can be expected to benefit, or not, from selected adjuvant therapy.

**Future rewards**

Clearly, genetic profile determination by techniques such as cDNA is more accurate than conventional tumour staging and is poised for rapid transfer from bench to the clinics. While extremely compelling, however, these data are not yet sufficient to call for basing routine therapeutic guidelines and policies in Canadian institutions on genetic signatures: larger retrospective and prospective trials that correlate treatment outcomes with tumour signatures are urgently needed. This expensive research will require dedicated teams of translational clinical researchers. The reward will be enormous: the ability to recommend the more intense, costly and toxic therapies only to appropriate individuals, with fewer patients treated but a higher proportion benefiting. Further, newly discovered genetic molecules will serve as templates for targeted approaches to diagnosis, treatment and prevention, as well as for curative treatments of established tumours. **CE**

**References**

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