



POST-SABCS Issue 3, 2013

**Association between the 21-Gene
Recurrence Score[®] and Benefit from
Adjuvant Paclitaxel in Node-Positive,
ER-Positive Breast Cancer**

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. This unique conference provides many clinicians and scientists from around the world a forum for discussing critical issues in the prevention and management of breast cancer. Therefore, SABCS is targeted by many members of the clinical research community as the optimal time to unveil new clinical data. This creates an environment in which yearly published results from a plethora of ongoing clinical trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes.

Although SABCS currently offers online access to the vast majority of the poster and plenary presentations from the annual meeting, the absence of expert assessment concerning practical applications may yield confusion among community oncologists who are challenged almost daily to appropriately apply a multitude of scientific findings across diverse tumors. Thus, identification of those data sets with immediate or impending relevance to the delivery of quality breast cancer care, in conjunction with professional commentary to address resultant practice ambiguity, may prove vastly beneficial to those physicians who are unable to make the annual pilgrimage to San Antonio. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS, including expert perspectives on how these new evidence-based concepts can and should be incorporated into on- and off-protocol patient care. This activity will assist medical oncologists, radiation oncologists, breast/general surgeons, nurses and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the EndoPredict® signature together with a predefined combination of clinicopathologic factors and molecular data as a predictor of late metastases for patients with estrogen receptor-positive and HER2-negative breast cancer.
- Assess the utility of the Oncotype DX® Recurrence Score® in predicting benefit from the addition of paclitaxel to adjuvant doxorubicin/cyclophosphamide for patients with lymph node-negative and estrogen receptor-positive breast cancer treated concurrently with endocrine therapy.
- Compare the performance of the Breast Cancer IndexSM biomarker to that of the Oncotype DX Recurrence Score and IHC4 score as prognostic factors for distant recurrence of hormone receptor-positive, lymph node-negative primary breast cancer.
- Determine the impact of metabolic syndrome on breast cancer recurrence for patients with high-, intermediate- or low-risk disease as defined by the 21-gene Oncotype DX Recurrence Score assay.
- Appraise the reproducibility of IHC-based Ki-67 biomarker assays and ongoing strategies to increase concordance in analysis and scoring methods.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee, Consulting Agreements and Speakers Bureau: Amgen Inc, Bristol-Myers Squibb Company, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Research Support: Genentech BioOncology, GlaxoSmithKline, Sanofi.

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This activity is supported by educational grants from Eisai Inc, Genentech BioOncology and Genomic Health Inc.

Hardware/Software Requirements:

A high-speed Internet connection

A monitor set to 1280 x 1024 pixels or more

Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later

Adobe Flash Player 10.2 plug-in or later

Adobe Acrobat Reader

(Optional) Sound card and speakers for audio

Last review date: April 2013

Expiration date: April 2014

Adjuvant chemotherapy for patients with node-positive luminal A breast cancer

To go directly to slides and commentary for this issue, [click here](#).

The December San Antonio Breast Cancer Symposium (SABCS) once again featured a bounty of papers focused on tissue predictors of response to systemic agents, and although none will shake up clinical practice like Dr Soon Paik’s legendary 2004 SABCS presentation documenting the predictive value of the 21-gene Recurrence Score® (RS) in tumor samples from patients on the NSABP-B-20 trial of tamoxifen alone or with chemotherapy (CT), on a macro level these translational and clinical findings contribute significantly to our knowledge base and help further divide this disease into specific biologic subsets. However, other than being an outlet for new research data, SABCS is also an exceptional educational event where fascinating sessions often provide new perspectives on patient care.

To that end, the spectacular clinical science symposium on the first day of the conference included a thoughtful and thought-provoking overview by Dr Kathy Albain on the critical and controversial issue of adjuvant treatment for patients with the common luminal A phenotype, defined by Dr Charles Perou and others as having high ER and normal HER2 levels and relatively low proliferation. Dr Albain noted that last year’s international meta-analysis demonstrated an overall benefit of CT in ER+ tumors, but the emergence of contemporary assays like the RS has now identified patients with ER+ tumors who are less likely to benefit from CT.

A critical issue in this regard is the patient with a node+ tumor, and to explore this Dr Albain took a unique tack by directly comparing the results of her work (presented in SABCS 2010) evaluating the RS in available tissue from the SWOG-8814 node+ study to the findings from Paik’s initial evaluation of the assay in node-negative tumors from B-20. Interestingly, there was a remarkably similar correlation between CT benefit and RS in B-20 and S8814. However, more than 2 years later

Remarkably Similar Significant Interaction between Chemotherapy Benefit and Recurrence Score in B20 and S8814

Variable/Study	Tamoxifen	Tamoxifen + Chemotherapy
10 yr DRFS B20 N0*		
Low Recurrence Score	97%	93%
High Recurrence Score	60%	73%
10 yr BCSS S8814 N+**		
Low Recurrence Score	93%	88%
High Recurrence Score	54%	73%

* Paik S, et al. J Clin Oncol 2006; interaction p = 0.038
 **Albain KS, et al. Lancet Oncol 2010; interaction p = 0.021

controversy still surrounds the issue. Dr Albain referred to a 2012 [JCO editorial](#) by Dr Dan Hayes in which he enthusiastically supported enrolling eligible patients on the ongoing RxPONDER node+ trial but vehemently objected to withholding CT (and the potential to improve the chance of remaining disease free) in such individuals outside a study setting. As is often the case with education sessions of this type, Dr Albain did not provide a definitive recommendation about the use of tissue predictors in node+ disease, but at [our CME symposium that evening](#) a number of the faculty members, including Drs Hal Burstein, Kim Blackwell, George Sledge and Cliff Hudis, noted that they will selectively obtain a RS in patients with node+, ER+, HER2-negative tumors and a low nodal burden.

After hearing Dr Albain's talk, I invited her to participate in an audio interview, during which she was particularly enthused about the next generation of prospective trials, including TAILORx and RxPONDER (RS in node-negative and node+ settings) and MINDACT and I-SPY 1 (70-gene signature in the adjuvant and neoadjuvant settings), which have the potential to drastically shift how predictive assays are employed in clinical practice. However, until these trials begin to report, oncologists must make these difficult decisions with a less than optimal evidence base and keep abreast of incremental steps forward. In that regard, here's the bottom line on the most recent crop of related SABCS data sets.

1. [More on RS in node+ tumors](#)

A prominent SABCS paper focused on another retrospective/prospective analysis of tissue in patients with ER+ tumors in a large Phase III trial (NSABP-B-28, evaluating AC alone or with paclitaxel in patients with node+ disease) and provided additional evidence that RS can predict outcome in this population. Interestingly, the incremental gain from paclitaxel was not correlated with RS, but the analysis was underpowered to make that determination.

2. Molecular profiles to predict risk of delayed recurrence (DR) in patients completing 5 years of adjuvant endocrine treatment

The SABCS presentation of the ATLAS trial of 5 versus 10 years of tamoxifen was yet another data set demonstrating the critical role of DR in ER+ tumors, and 2 early but encouraging papers reported on novel RT-PCR assays to identify patients at particular risk for these events. The first looked at the ["EndoPredict® Score"](#) in tissue from 2 major Austrian trials, and the second examined the ["Breast Cancer Index"](#) versus RS and IHC4 in 665 primary tumor samples from the TransATAC tissue bank. Although not definitive, it appears that these or other similar assays may one day be able to provide important input on the critical clinical decision of extending endocrine treatment to 10 years or more while also yielding clues about specific genes correlated with the almost mysterious syndrome of DR, particularly in luminal A tumors.

3. Another dagger in the heart of Ki-67

Show this abstract to your friendly local pathologist the next time he or she offers a home brew that can save you the cost of a RS. After reviewing these scary numbers on lack of Ki-67 reproducibility among pathologists, unless perhaps Dr Mitch Dowsett or Dr Matt Ellis is doing your assay, you may want to rethink this approach.

4. Correlation between metabolic syndrome (MS) and breast cancer recurrence in luminal A tumors

This fascinating effort from Dr Albain's group attempted to determine whether the presence of MS is predictive of breast cancer recurrence in RS subtypes. In addition to documenting an overall eye-popping 27% rate of MS (glucose intolerance/diabetes and 2 other factors, including hypertension, dyslipidemia, central obesity and microalbuminemia) among the 332 patients in the study, of great interest was the correlation of MS and recurrence rate in patients with low RS. This intriguing finding suggests that the work of Dr Rowan Chlebowski and many others demonstrating a link between recurrence and metabolic factors like diet, obesity and exercise may be particularly relevant in luminal A tumors.

Next on this series: SABCS papers on CT, including a surprising potentially practice-changing paper on "pseudoadjuvant" treatment for patients with resected local recurrences rendered Stage IV with no evidence of disease.

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Association between the 21-Gene Recurrence Score and Benefit from Adjuvant Paclitaxel in Node-Positive, ER-Positive Breast Cancer

Presentation discussed in this issue

Mamounas EP et al. **Association between the 21-gene Recurrence Score (RS) and benefit from addition of adjuvant paclitaxel in node-positive, ER-positive breast cancer patients: Results from NSABP B-28.** San Antonio Breast Cancer Symposium 2012; **Abstract S1-10.**

Slides from a presentation at SABCS 2012 and transcribed comments from recent interviews with Clifford Hudis, MD (1/11/13) and Lisa A Carey, MD (1/17/13)

Association between the 21-Gene Recurrence Score (RS) and Benefit from Addition of Adjuvant Paclitaxel in Node-Positive, ER-Positive Breast Cancer Patients: Results from NSABP B-28

Mamounas EP et al.

Proc SABCS 2012;Abstract S1-10.

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Background

- The 21-gene Oncotype DX[®] Recurrence Score[®] (RS) assay predicts the 10-year risk of distant recurrence and survival in lymph node (LN)-negative and LN-positive, ER-positive breast cancer (BC) treated with adjuvant endocrine therapy (*Breast Cancer Res Treat* 2011;127:133).
- The RS predicts benefit from chemotherapy in patients with ER-positive BC (*Lancet Oncol* 2010;11:55).
- In addition, the RS predicts the risk of death for patients with ER-positive BC with ≤ 3 positive nodes that has been treated with adjuvant chemoendocrine therapy (*Breast Cancer Res Treat* 2012;134:683).
- **Study objective:** To evaluate the association between the RS and benefit of adding paclitaxel (P) to doxorubicin/cyclophosphamide (AC) therapy for patients with LN-positive, ER-positive BC from the NSABP-B-28 trial.

Mamounas EP et al. *Proc SABCS* 2012;Abstract S1-10.

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Study Methods

- The Phase III NSABP-B-28 trial compared 4 cycles of AC to AC → P, and patients younger than 50 years or 50 and older with hormone receptor-positive BC also received tamoxifen for 5 years with concurrent chemotherapy (n = 3,060).
- This subset analysis of NSABP-B-28 included patients with ER-positive BC by central microarray IHC assay and with successful 21-gene RS assay results (n = 1,065).
 - Patients who received AC: 519
 - Patients who received AC → P: 546
- Kaplan-Meier estimates and log-rank tests were used to assess survival outcomes in patient subgroups by RS and treatment.
- Multivariate Cox regression models were adjusted for traditional clinicopathologic factors and used to determine the predictive utility of adding paclitaxel to AC (AC → P).

Mamounas EP et al. *Proc SABCS* 2012;Abstract S1-10.

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Analysis of Prognosis by RS Risk Groups (10-Year Follow-Up)

Outcome	Low risk (n = 386)	Interm risk (n = 364)	High risk (n = 315)	p-value
DFS	75.8%	57.0%	48.0%	<0.001
DRFI	80.9%	64.9%	55.8%	<0.001
OS	90.0%	74.7%	63.0%	<0.001
BCSS	95.0%	78.9%	68.2%	<0.001

Interm = intermediate; DFS = disease-free survival; DRFI = distant recurrence-free interval; OS = overall survival; BCSS = BC-specific survival

- The distribution of patients by RS was not significantly different according to treatment, surgery type and number of positive nodes.
- There were statistically significant differences in the distribution of the RS according to age and tumor size:
 - Older patients and those with small tumors were more likely to have a low RS.

Mamounas EP et al. Breast Cancer Symposium 2012;Abstract 1; Mamounas EP et al. Proc SABCS 2012;Abstract S1-10.

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Benefit of Adding P to AC (10-Year Follow-Up)

Outcome	AC (n = 519)	AC → P (n = 546)	HR	p-value
DFS	58.9%	63.2%	0.87	0.14
DRFI	66.4%	69.6%	0.89	0.26
OS	74.9%	78.5%	0.87	0.26

HR = hazard ratio

Mamounas EP et al. Proc SABCS 2012;Abstract S1-10.

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DFS and DRFI: Benefit of Adding P to AC by RS Risk Group (10-Year Follow-Up)

DFS*	AC	AC → P	HR	p-value
Low risk (n = 186, 200)	75.5%	76.1%	1.01	0.99
Interm risk (n = 180, 184)	53.4%	60.4%	0.84	0.26
High risk (n = 153, 162)	45.3%	50.5%	0.81	0.21
DRFI†	AC	AC → P	HR	p-value
Low risk (n = 186, 200)	80.8%	80.9%	0.95	0.78
Interm risk (n = 180, 184)	62.5%	67.3%	0.88	0.49
High risk (n = 153, 162)	53.2%	58.2%	0.86	0.40

* Test for common treatment benefit of adding paclitaxel to AC ($p = 0.65$)

† Test for common treatment benefit of adding paclitaxel to AC ($p = 0.93$)

Mamounas EP et al. *Proc SABCS 2012*;Abstract S1-10.

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OS Benefit of Adding P to AC by RS Risk Group (10-Year Follow-Up)

OS*	AC	AC → P	HR	p-value
Low risk (n = 186, 200)	91.5%	88.5%	1.28	0.40
Interm risk (n = 180, 184)	69.9%	79.3%	0.74	0.12
High risk (n = 153, 162)	60.7%	65.3%	0.86	0.45

* Test for common treatment benefit of adding paclitaxel to AC ($p = 0.30$)

Mamounas EP et al. *Proc SABCS 2012*;Abstract S1-10.

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Author Conclusions

- The 21-gene RS significantly predicted risk of recurrence and death for patients with LN-positive and ER-positive BC treated with adjuvant chemoendocrine therapy.
- The RS did not significantly predict benefit from the addition of paclitaxel to AC among 1,065 patients from the NSABP-B-28 trial with ER-positive BC included in this analysis:
 - A possible explanation may be that the overall benefit from paclitaxel was small and statistical power to detect treatment by RS interaction was low.
 - An insignificant trend was observed toward benefit with the addition of paclitaxel to AC for patients with intermediate and high RS results.
- Future studies are planned to identify new genes that may be used to predict taxane benefit.

Mamounas EP et al. *Proc SABCS 2012*;Abstract S1-10.

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Investigator Commentary: Association between the 21-Gene RS and Benefit from Adding P to AC in LN-Positive, ER-Positive BC

This is a subset study of prognosis for patients with ER-positive, LN-positive BC who had received tamoxifen with concurrent chemotherapy (CT) on the NSABP-B-28 trial. The RS is known to be prognostic for LN-positive BC, but this study determined whether it could predict benefit from adding CT. It demonstrated that the RS is a good prognostic tool when patients are classified according to RS risk groups. The DFS was 75% for patients in the low-risk group and 48% in the high-risk group. However, analysis of RS as a predictor of benefit from adding P to AC was not statistically significant. There was a hint that in the low-risk group patients didn't gain much with additional CT, but the interaction term wasn't significant and it's not certain that the RS can be used in that way. Nevertheless, I believe it's an excellent prognostic tool. I believe these results do add to our comfort level that this tool is prognostic whether you have administered endocrine therapy or have added chemotherapy, whether the BC is node-negative or node-positive. The "devil is in the details" of figuring out how exactly it helps to make decisions.

Interview with Lisa A Carey, MD, January 17, 2013

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