



POST-SABCS Issue 3, 2013

Metabolic Syndrome and Recurrence According to the 21-Gene Recurrence Score[®] in Node-Negative 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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Chief, Division of Hematology and Oncology
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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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Metabolic Syndrome and Recurrence According to the 21-Gene Recurrence Score in Node-Negative Breast Cancer

Presentation discussed in this issue

Lakhani A et al. **Metabolic syndrome and recurrence within the 21-gene Recurrence Score assay risk categories in lymph node negative breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract PD10-02.**

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

Metabolic Syndrome and Recurrence within the 21-Gene Recurrence Score Assay Risk Categories in Lymph Node Negative Breast Cancer

Lakhani A et al.

Proc SABCS 2012;Abstract PD10-02.

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Background

- Metabolic syndrome (MS) refers to a constellation of abnormalities similar to those of diabetes, a disease linked to breast cancer (BC).
- Evidence shows that the incidence of MS is increasing, but its interaction with BC incidence, tumor biology and outcomes are not fully understood (*Am J Clin Nutr* 2007;86:s823).
- The Oncotype DX[®] Recurrence Score[®] (RS) assay quantifies the probability of disease recurrence in early-stage estrogen receptor (ER)-positive BC and has prognostic and predictive significance (*Lancet Oncol* 2010;11:55).
- **Study objective:** To determine whether the presence of MS is predictive of BC recurrence to a variable degree across the different BC types as defined by the risk categories of the 21-gene Oncotype DX RS assay.

Lakhani A et al. *Proc SABCS* 2012;Abstract PD10-02.

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Study Methods

- The study included patients with newly diagnosed ER-positive, lymph node (LN)-negative BC treated between 2006 and 2011 who underwent a 21-gene RS assay (n = 332).
- All patients received standard systemic/local therapy.
- The electronic medical record was searched for key diagnoses including MS, and patients were classified into MS groups using the World Health Organization (WHO) definition.
- Tumor characteristics including grade, size, Ki67 and HER2 status were recorded.
- Patient characteristics including age, race, menopausal status and body mass index were recorded.
- The association of MS, tumor and patient characteristics within the RS risk groups was analyzed.

Lakhani A et al. *Proc SABCS* 2012;Abstract PD10-02.

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Overview of Patient Characteristics and Study Outcomes

Characteristic	n = 332
Median age	62 years
Patients with MS	27%

- The WHO classification defines MS as diabetes mellitus or glucose intolerance in addition to at least 2 of the following: hypertension, dyslipidemia, central obesity and microalbuminemia.
- Out of 21 patients with recurrent BC, 13 (61.9%) had MS.
- A significant association was evident between BC recurrence and MS, independent of other factors ($p = 0.0002$).
- A significant association was evident between MS and race ($p = 0.004$).
- No significant association was apparent between MS and any of the other patient or tumor characteristics studied, including the 21-gene RS.

Lakhani A et al. *Proc SABCS 2012*;Abstract PD10-02.

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Effect of MS on BC Recurrence

Oncotype DX risk category	Odds ratio (presence vs absence of MS)	95% CI
Low risk (RS 0-17)	23.649	2.818-198.435
Intermediate risk (RS 18-30)	3.950	0.984-15.852
High risk (RS 31-100)	0.813	0.063-10.478

- A significant association was evident between BC recurrence and MS in patients with BC categorized as low risk by the Oncotype DX RS score.

Lakhani A et al. *Proc SABCS 2012*;Abstract PD10-02.

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Analysis of MS According to Race

Race	MS		p-value*
	Presence	Absence	
Caucasian (n = 284)	24%	76%	0.0081
African American (n = 21)	52%	48%	
Hispanic (n = 11)	36%	64%	
Asian (n = 9)	44%	56%	
Other (non-Hispanic) (n = 1)	100%	0%	

* Chi-squared *p*-value

Lakhani A et al. *Proc SABCS 2012*;Abstract PD10-02.

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Author Conclusions

- MS is an independent risk factor for BC recurrence among women with LN-negative, ER-positive, low-risk BC treated with standard adjuvant therapy.
- MS has an impact on recurrence for patients with a tumor biology defined by the 21-gene *Oncotype DX RS* assay as low risk or, to a lesser extent, intermediate risk.
- However, there is no difference in recurrence risk for patients at high risk using the *Oncotype DX RS* assay.
- Interventions directed at modifying MS in patients with newly diagnosed early BC have the potential to favorably affect survival for those with specific tumor characteristics.
- Prospective studies should be conducted to further evaluate the short- and long-term effects of MS on BC outcomes.

Lakhani A et al. *Proc SABCS 2012*;Abstract PD10-02.

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Investigator Commentary: Impact of Metabolic Syndrome on BC Recurrence Using the 21-Gene Oncotype DX Recurrence Score

The study started with 332 patients with ER-positive, LN-negative BC, of which 89 had MS according to the WHO criteria. A patient with MS must have diabetes or glucose intolerance in addition to 2 or more of hypertension, dyslipidemia, central obesity or microalbuminemia, several of which have been independently associated with poorer outcome. One finding was that MS was associated with race, with 52% of the African American study population having MS compared to 24% of Caucasians. With this study design it will be difficult to determine the condition driving poorer outcome. Although a multivariate analysis was performed, it was limited by the inclusion of only 89 patients. If race is the driving factor, it is important to note that it is associated with negative prognostic implications. Although use of the Oncotype DX RS to study the relationship between MS and BC recurrence didn't add to our understanding in terms of disease outcome, this is an interesting and hypothesis-generating study.

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

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