5 Minute JournalClub

Prognostic and Predictive Value of the 21-Gene Recurrence Score® for Women with Node-Positive Breast Cancer Receiving Chemotherapy

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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. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. 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 meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Identify the prognostic and predictive value of the 21-gene Recurrence Score for chemotherapy benefit in postmenopausal women with node-positive and ER-positive breast cancer.

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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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IN THIS ISSUE:

- **SWOG analysis** again demonstrates lack of benefit of adjuvant chemotherapy for patients with node-positive tumors and low Recurrence Scores®
- **Survey demonstrates** similar clinical practice impact of Onco*type* DX for patients with node-positive tumors to that previously seen with node-negative tumors
- **Onco*type* DX results from core biopsies** similar to those from excisional biopsies

The current Phase III adjuvant breast cancer research platform to a great extent was shaped by the deep passion and commitment of two legendary clinical investigators, the NSABP's Dr Bernard Fisher and Dr Gianni Bonadonna from the Milan Cancer Institute. Bernie was actually the first person interviewed when the *Breast Cancer Update* audio series was launched in 1988, and not long after, I met up with the very suave Dr Bonadonna, who resembled a classic Italian movie star much more than a world-class scientist. Beginning in the late 1960s, these fiery and inspirational leaders persuaded an international audience to support clinical trials evaluating the then-heretical idea of giving chemotherapy to patients who might already be cured. Bonadonna managed to obtain support for the logical approach of adjuvant combination chemotherapy (CMF), while Bernie struggled just to study L-PAM.

At this year's San Antonio meeting I met Dr Bonadonna's protégé, Dr Luca Gianni, who last year at the meeting presented the NOAH study that was just published in the *JCO* and demonstrated Buzdar-like results of neoadjuvant chemo with a trastuzumab/anthracycline-containing regimen for locally advanced HER2-positive disease. With the excellent Italian research infrastructure developed by Dr Bonadonna and others, including Dr Umberto Veronesi, Dr Gianni has led a number of important studies of pre-op therapy, including one of the few to investigate Onco*type* DX as a predictor of response to neoadjuvant chemotherapy. (As one might guess, it predicted path CRs.) At the end of our chat, Dr Gianni casually mentioned that his cooperative group (Fondazione Michelangelo) was running a trial randomizing patients with ER-positive, HER2-negative, node-positive tumors and low Recurrence Scores to hormone therapy alone or preceded by chemotherapy.

Upon hearing these words, I swallowed and asked, just to be sure: "So this is essentially a TAILORx-like study for patients with node-positive tumors?" His answer was simply, "Yes." Walking back to the "Marriott attached to the mall," I ran into Dan Hayes and asked if he knew that the Italians had pulled off what the US cooperative groups had been trying to implement since Kathy Albain presented the initial 2007 San Antonio SWOG node-positive data set on Onco*type* DX. It was news to Dan, who seemed frustrated by the glacier-like trial development and review process in the United States.

Meanwhile, *Lancet Oncology* had teamed up with Dr Albain, the SWOG investigators and San Antonio and arranged to publish electronically the definitive "node-positive" Onco*type* paper at 5:30 PM CST, the moment that Dr Christos Sotiriou walked to the podium on the first day of the meeting to discuss the poster findings. This new SWOG analysis has the same message as the initial one: Patients with low and maybe intermediate Recurrence Score tumors don't seem to benefit from chemotherapy. However, there is uniform support for a prospective trial very much like the one Dr Gianni described that will attempt to prospectively validate the clinical utility of the Recurrence Score for patients with node-positive tumors.

Our Patterns of Care surveys show that US-based oncologists are already using Onco*type* DX for some patients with node-positive tumors, and this new data set is likely to increase reliance on this practice-changing assay. Hopefully, the test will help guide physicians to enroll their patients with node-positive, low Recurrence Score tumors on clinical trials of novel therapies that might lower the risk of disease progression. This shouldn't be too difficult with the current PARP inhibitor mania and other promising approaches, such as the use of high-dose megestrol acetate to stimulate production of the NM23-H1 antimetastatic factor. One might also envision the utility of Onco*type* DX for some older patients or those with comorbidities, with node-positive tumors and high Recurrence Scores who might otherwise be inclined to skip treatment but might reconsider with an assay predicting high efficacy.

What's maybe even more important is what can be accomplished with an appropriate community-based research infrastructure and effective leadership as demonstrated by the Milan group and, for that matter, by the Austrians, whose zoledronic acid adjuvant study was among the most important new data sets in the field in recent years. Drawing from a smaller population than in the state of Florida, the Milan group believes it can complete what is most definitely a landmark study. To get results quicker, maybe the NSABP should consider joining in. It would be the perfect partnership, considering how these two groups and their founding fathers truly helped move the field forward for the benefit of patients.

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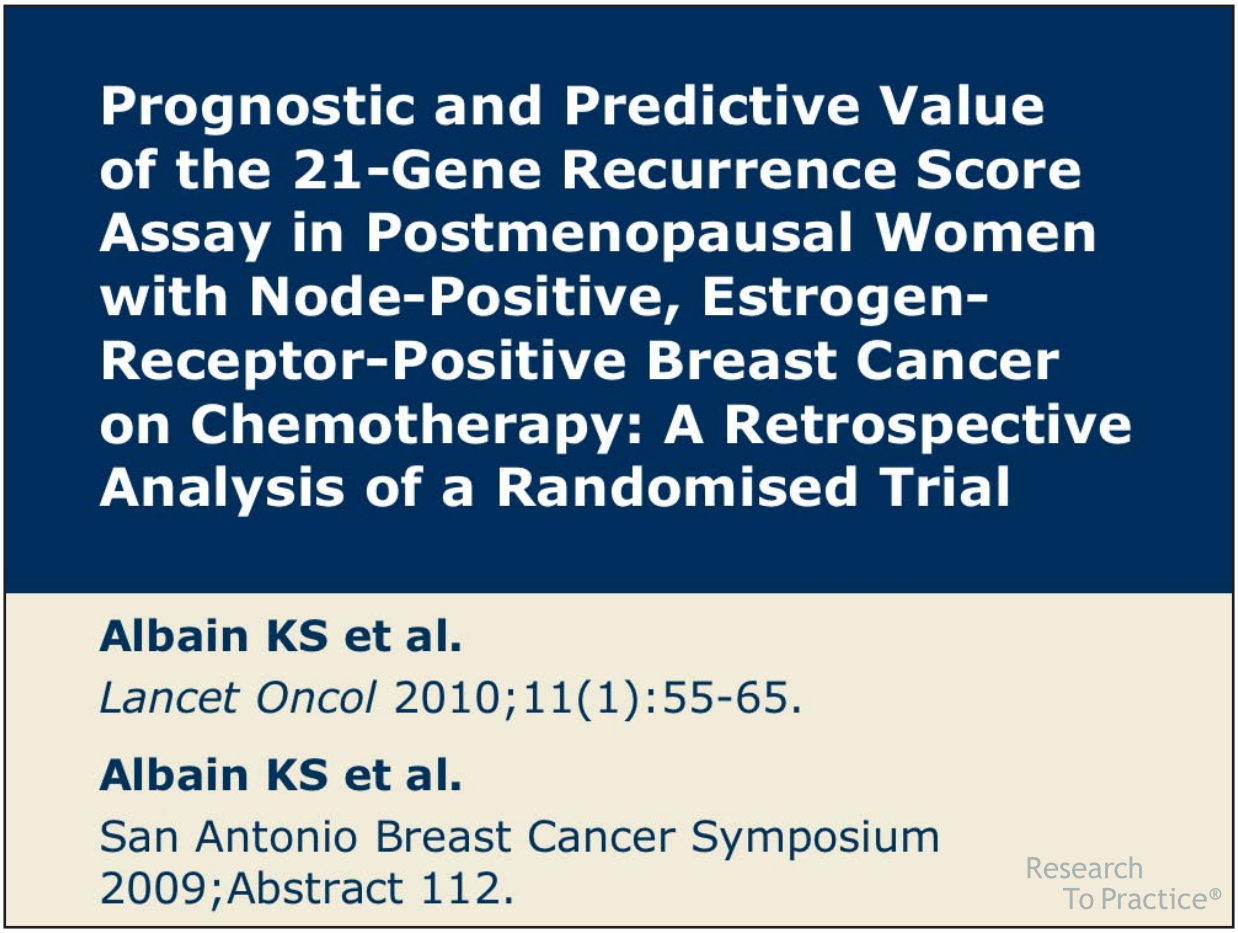
Prognostic and Predictive Value of the 21-Gene Recurrence Score® for Women with Node-Positive Breast Cancer Receiving Chemotherapy

Presentation discussed in this issue

Albain KS et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomized trial.** *Lancet Oncol* 2010;11(1):55-65. **Abstract**

Slides from a journal article and transcribed comments from Joseph A Sparano, MD (1/20/10) at a closed roundtable meeting and a recent interview with Adam M Brufsky, MD, PhD (12/23/09)



Introduction

- A low 21-gene recurrence score (RS) in postmenopausal patients with ER-positive, node-negative breast cancer predicts a lack of benefit from the addition of chemotherapy to tamoxifen (T) treatment (*JCO* 2006;24:3726).
- The value of the 21-gene recurrence score assay in patients with ER-positive, node-positive breast cancer that are treated with T alone is unknown.
- **Current study objectives:**
  - Assess prognostic value of the 21-gene recurrence score in patients with node-positive breast cancer treated only with T.
  - Assess whether 21-gene recurrence assay allows for the prediction of a node-positive subset of patients who do not benefit from anthracycline-based chemotherapy.

Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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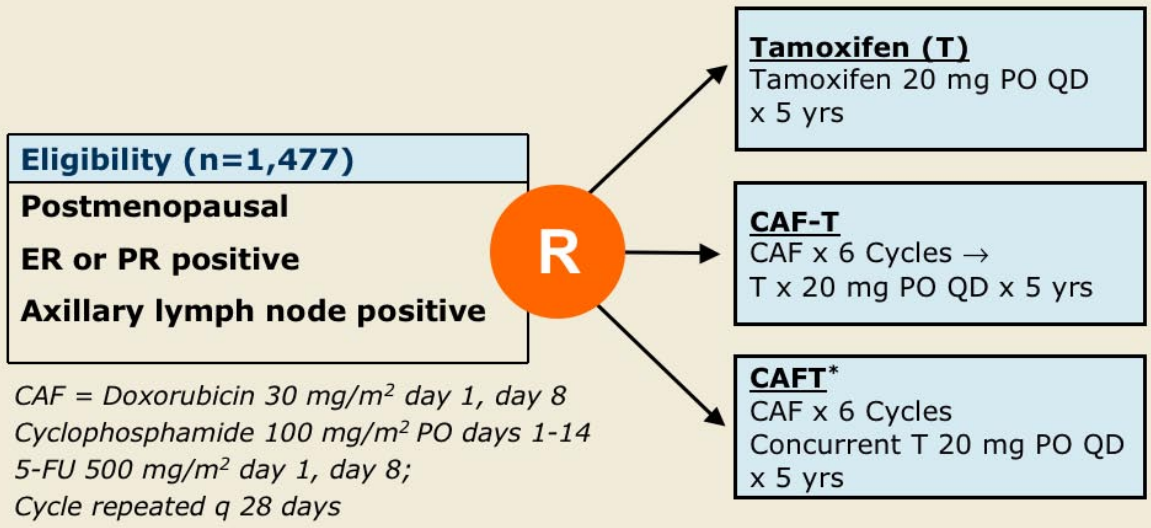
SWOG-8814: Parent Trial Schema



CAF = Doxorubicin 30 mg/m² day 1, day 8
Cyclophosphamide 100 mg/m² PO days 1-14
5-FU 500 mg/m² day 1, day 8;
Cycle repeated q 28 days

* Excluded from analysis due to inferior efficacy

Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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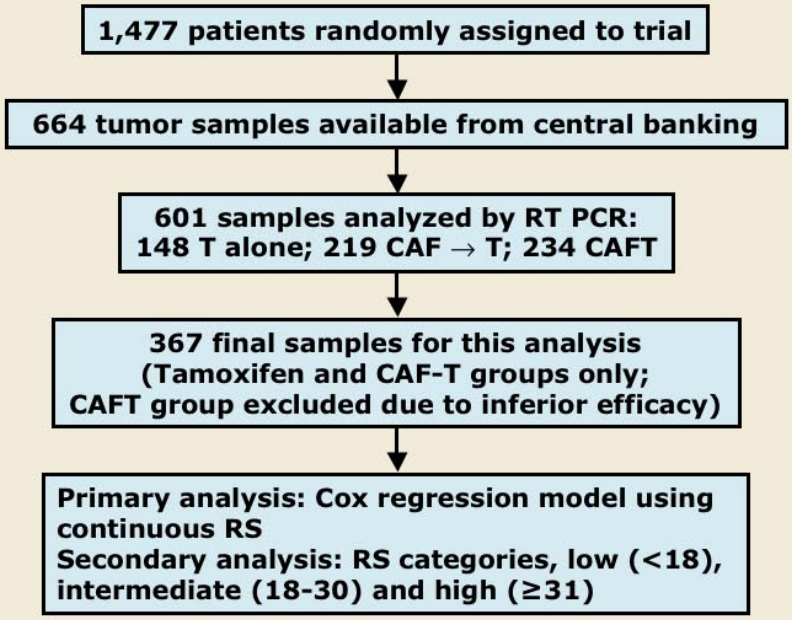
SWOG-8814: Translational Study



Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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Ten-Year Disease-Free Survival (DFS) and Overall Survival (OS) in Tamoxifen Alone Group

RS Group	10-year DFS	DFS *p*-value*	10-year OS	OS *p*-value*
Low (<18)	60%	0.017	77%	0.003
Intermediate (18-30)	49%		68%	
High (≥31)	43%		51%	

*Log-rank *p*-value stratified according to the number of positive nodes (1-3 vs ≥4 positive nodes).

Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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Hazard Ratio: Ten-Year DFS, T versus CAF-T Groups

RS Group	HR (95% CI)	*p*-value*
Low (<18)	1.02 (0.54-1.93)	0.97
Intermediate (18-30)	0.72 (0.39-1.31)	0.48
High (≥31)	0.59 (0.35-1.01)	0.033
Entire RS sample	—	0.054

*Log-rank *p*-value stratified according to the number of positive nodes (1-3 vs ≥4 positive nodes); HR = hazard ratio.

Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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Conclusions

- The RS is prognostic for patients with node-positive breast cancer treated with tamoxifen alone.
- A high RS score predicts an improved DFS in patients with node-positive breast cancer treated with anthracyline-based chemotherapy followed by tamoxifen compared to tamoxifen alone.
- A low RS score identifies women with node-positive breast cancer who may not benefit from the addition of anthracycline-based chemotherapy to tamoxifen treatment.

Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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Conclusions (Continued)

"Prospective studies with larger sample sizes are essential to establish who benefits most from modern endocrine therapy plus chemotherapy, and whether use of multigene assays affects survival."

- KS Albain

Albain KS et al. *Lancet Oncol* 2010;11(1):55-65.

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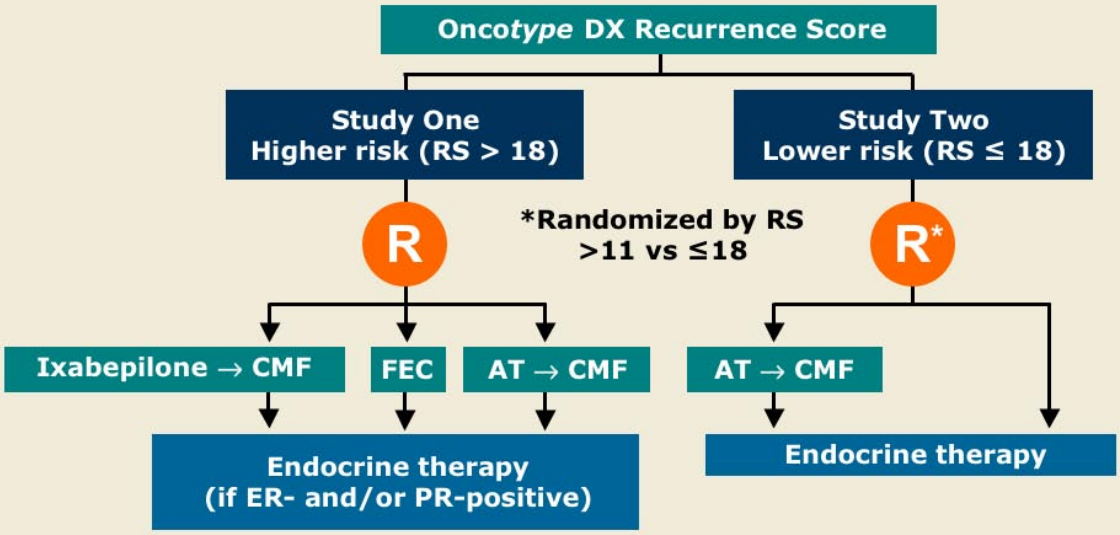
Fondazione Michelangelo Phase III Trial in HER2-Negative Conventionally High-Risk Patients (Node-Positive and/or T2-T3)



Gianni L. Personal Communication. December 2009; Gianni L. Presentation. Research To Practice Satellite Symposium, San Antonio Breast Cancer Symposium 2009; www.fondazionemichelangelo.org.

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DR SPARANO: This is an important follow-up of a paper that's already been presented previously in 2007. There are two principles to keep in mind when examining this paper.

The first is the notion of nodal status as a prognostic factor. Nodal status, unlike Recurrence Score (RS) or some of these other multigene factors, is really a time-dependent variable. Multigene profiles are generally static variables and represent a snapshot of the biology of the disease at that particular moment. The degree of nodal involvement is dependent upon not only the biology of the disease but also on how long the disease has been present. It is also likely a surrogate for the amount of micrometastatic disease present. That has been shown nicely in other work — that patients with node-positive disease have a higher disseminated tumor cell prevalence than patients with node-negative disease.

The second principle is that in the few trials that have examined how well multigene parameters correlate with clinical features, it seems that the two correlate very poorly with each other. What that indicates is that they're really measuring different things.

The parent SWOG-8814 trial targeted postmenopausal women who had node-positive, ER-positive disease. They were randomly assigned to tamoxifen versus tamoxifen plus CAF chemotherapy, either concurrently or sequentially, followed by tamoxifen. This analysis was restricted to those who were assigned to tamoxifen alone versus CAF followed sequentially by tamoxifen, which was an arm that did better than the concurrent tamoxifen arm. They examined a subset of patients enrolled in the trial, about 40 percent of the parent trial, a relatively small sample size of 367 patients.

DR BRUFSKY: The RS was a greater predictor than anything else examined — greater than having one to three positive nodes, greater than having four positive nodes. That is the main finding of this paper. In the low-RS subset of women with node-positive disease, no matter how many positive nodes they have, patients are just not going to benefit from receiving chemotherapy, and these patients appear to obtain substantial benefit just from hormonal therapy.

DR SPARANO: The results were similar to what had been previously reported in the B-20 trial, which looked at patients with ER-positive, node-negative disease treated with tamoxifen or tamoxifen plus CMF. The benefit of chemotherapy seemed to be restricted to those who had a high RS. A statistically significant benefit was not seen in those who had a low RS or an intermediate RS, although in both studies there seemed to be a slight trend favoring the use of chemotherapy in that group.

DR BRUFSKY: The take-home message for me as an oncologist is that I am going to do this assay on women with node-positive breast cancer, at least postmenopausal women. The typical kind of woman who you're going to see as a patient — around 65 to 70 years old with ER-positive breast cancer and two or three positive nodes — should have this assay done in my opinion. There are also the patients who are

strongly averse to chemotherapy. If you perform the Onco*type* DX® assay on these patients and they have a low RS of less than 18, you now have some data to support administering only endocrine therapy. The results of this study reinforce that.

DR SPARANO: I think this study provides reassurance that the RS can be potentially useful for patients who have node-positive disease, and it might be useful in selecting individuals who may not benefit from chemotherapy. We are talking about a small data set, however, and it would be reassuring to see more data.

Now that the approval for the Onco*type* DX assay has been expanded to include patients who have node-positive disease, it makes me feel more comfortable about using the assay in older patients who have low-volume node-positive disease and using the assay as a means to spare administering chemotherapy to patients to whom I would have otherwise recommended chemotherapy.

Editor's Note: As mentioned in the cover email, a new clinical trial from the Fondazione Michelangelo will prospectively assess the use of Onco*type* DX in patients with node-positive and larger tumors.

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