# 5 Minute JournalClub

POST-SABCS Issue 1, 2013

# S1207 Trial of Adjuvant Endocrine Therapy with or without Everolimus for High-Risk, Hormone Receptor-Positive, HER2-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

- Apply the results of emerging research evaluating the optimal dose of fulvestrant to the clinical care of postmenopausal patients with locally advanced or metastatic breast cancer.
- Evaluate the contributory effects of bevacizumab when added to standard endocrine therapy for postmenopausal patients with unresectable, locally advanced or metastatic breast cancer.
- Integrate new clinical trial data supporting the extended use of adjuvant tamoxifen beyond 5 years to the treatment of patients with localized estrogen receptor-positive breast cancer.
- Describe the rationale for and emerging efficacy and tolerability data with the novel combination of endocrine therapy and a cyclin-dependent kinase 4/6 inhibitor for postmenopausal women with hormone receptor-positive advanced 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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No real or apparent conflicts of interest to disclose. Prof Peto was not paid for his interview.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

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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: February 2013
Expiration date: February 2014

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POST-SABCS Issue 1, 2013

# SABCS highlights: Should adjuvant tamoxifen now be administered for 10 years?

To go directly to slides and commentary for this issue, **click here**.

In 1995 the National Cancer Institute (NCI) mailed a "Clinical Alert" to oncologists strongly cautioning them to limit the duration of adjuvant tamoxifen (TAM) to 5 years based on data from NSABP and Scottish trials demonstrating no advantage and perhaps a detriment with prolonged endocrine treatment. While investigators worldwide endorsed this recommendation, legendary Oxford statistician Sir Richard Peto and his cadre were not convinced and regularly noted (most memorably in a fiery exchange during the 2000 NIH/NCI Breast Cancer Consensus Conference) that the available data on TAM duration were inadequately powered to answer the question. Further, they believed there was a substantial likelihood that longer treatment would yield greater benefit and to that end championed the launch of 2 massive international trials — ATLAS and **aTTom** — comparing 5 years to 10 years of TAM.

More than a decade later, this past December during the San Antonio Breast Cancer Symposium, Peto (as usual) had the last word when his colleague Richard Gray presented the dramatic findings from the ATLAS trial demonstrating a clear-cut and meaningful advantage in favor of continuing TAM for 10 years. As ATLAS was quite likely the biggest story coming out of the meeting by the river, we decided to kick off this year's post-SABCS series by profiling that and other endocrine-related papers:

**1. ATLAS (10 versus 5 years of adjuvant TAM)**

Perhaps the most fascinating aspect of this historic study is how ER-positive disease evolves over time and the impressive carryover effect of endocrine treatment that persists for up to a decade after discontinuation. Several weeks after San Antonio, in another in a series of audio interviews I've done with Dr Peto stretching back more than 20 years, he emphasized the profound delayed impact of adjuvant hormonal therapy and pointed out that the full measure of benefit of 10 years of TAM won't be determined until about 2018.

Although more follow-up is welcome, it also seems that there is now a rapidly developing consensus based on the ATLAS findings that treatment should be continued

out to 10 years in patients who remain premenopausal after 5 years of TAM. Treatment for patients who become menopausal during the first 5 years of TAM is far less clear cut, but switching to an aromatase inhibitor and continuing therapy is another logical option. For postmenopausal women with an intact uterus, the risk-benefit profile of 10 years of TAM is controversial.

**2. Encouraging data with letrozole in combination with a cyclin-dependent kinase (CDK) inhibitor**

CDKs play a critical role in regulating cell-cycle progression, and laboratory evidence suggests possible synergy between CDK inhibition and endocrine treatment. Those observations led to a randomized Phase II trial in postmenopausal women comparing the CDK inhibitor PD 0332991 combined with letrozole to letrozole alone, which at San Antonio demonstrated an improvement in progression-free survival (PFS) from 7.5 to 26.1 months in favor of the combination, with minimal additional toxicity, mainly myelosuppression. Although there was considerable excitement surrounding these impressive results, all agree that a Phase III trial will determine if this is for real or just iniparib-esque hype that will lead to disappointment.

**3. Survival benefit of 500 mg vs 250 mg fulvestrant**

With an overall survival (OS) hazard rate of 0.81, this is one of the few Phase III breast cancer trials of any type that shows that dose really can matter. The study supports the current widely used practice of administering 500-mg fulvestrant, and one wonders if this fascinating agent will ever be studied in an adjuvant trial.

**4. Bevacizumab (bev) and endocrine treatment for metastatic disease (LEA trial)**

Same old story here as this Phase III study demonstrated a modest trend for PFS benefit in favor of bev without any effect on survival. This leads to a logical question: Is this the end of the line for anti-angiogenic agents in breast cancer until the ECOG adjuvant bev trial results mature? The answer is not as simple as you might think given the **surprising positive trial results recently reported in metastatic gastric cancer** showing a PFS and OS advantage for monotherapy with a monoclonal antibody to the VEGF receptor 2 (ramucirumab) suggesting that we may not have seen the end of positive research findings with this strategy.

**5. SWOG-S1207: Adjuvant everolimus with endocrine treatment**

This important study, highlighted during the conference's ongoing clinical trials session, supports the notion that "the best clinical option is often trial participation." Many patients with ER-positive, HER2-negative tumors have less than optimal long-term outcomes with endocrine treatment and chemotherapy, and this study allows patients

the opportunity to maybe fare better by adding an agent with encouraging supportive data in the metastatic setting.

Next in this series: Metastatic HER2-positive disease — where the world awaits the much-needed approval of the antibody-drug conjugate trastuzumab emtansine (T-DM1), and we review more data from San Antonio on the other major recent addition to the field, the HER2 dimerization inhibitor pertuzumab.

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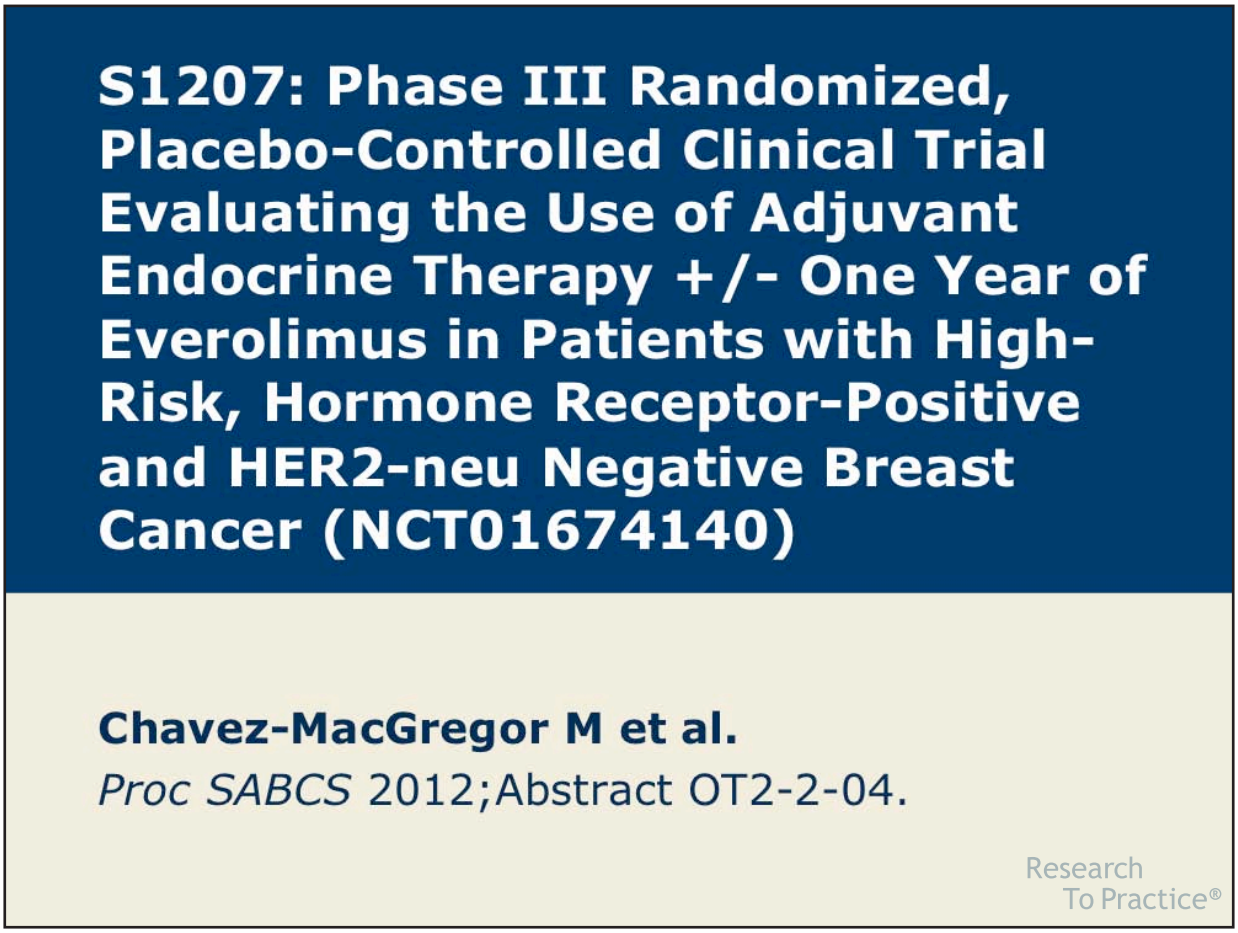
# S1207 Trial of Adjuvant Endocrine Therapy with or without Everolimus for High-Risk, Hormone Receptor-Positive, HER2-Negative Breast Cancer

## Presentation discussed in this issue

Chavez-MacGregor M et al. **S1207: Phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy +/- one year of everolimus in patients with high-risk, hormone receptor-positive and HER2-neu negative breast cancer (NCT01674140).** San Antonio Breast Cancer Symposium 2012;**Abstract OT2-2-04**.

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



# Background

- The PI3K/AKT/mTOR signaling pathway has been associated with resistance to endocrine therapies (ETs) in hormone receptor (HR)-positive breast cancer (BC) (*Int J Cancer* 2006;118(2):284).
- Everolimus is an mTOR inhibitor that has been shown to increase progression-free survival when combined with aromatase inhibitors (*N Engl J Med* 2012;366(6):520).
- Everolimus in combination with tamoxifen increased the time to disease progression among patients with metastatic BC previously treated with aromatase inhibitors (*J Clin Oncol* 2012;30(22):2718).

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

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# SWOG-S1207 Study Objectives

- **Primary objective:** To determine whether 1 year of everolimus in combination with standard adjuvant ET improves invasive disease-free survival (IDFS) for patients with high-risk, HR-positive, HER2-negative BC.
- **Secondary objectives include:**
  - Overall survival (OS)
  - Distant recurrence-free survival
  - Safety and toxicity
  - Quality of life
  - Collection of specimens for translational studies
  - Evaluation of adherence

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

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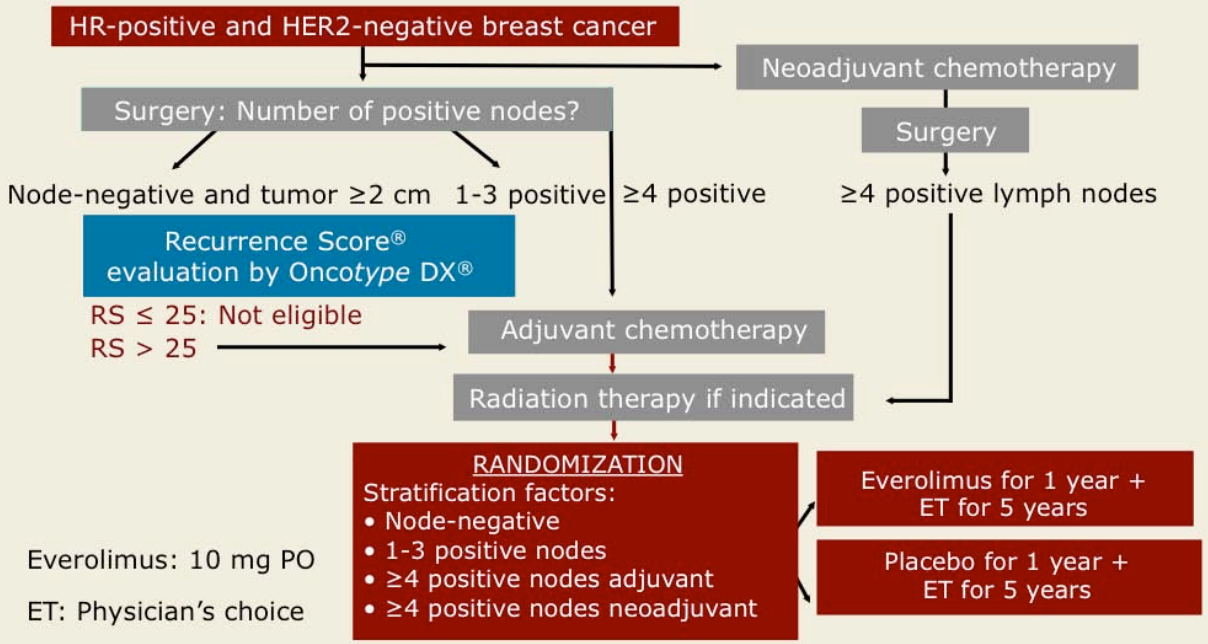
# Phase III SWOG-S1207 Trial Design




Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

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# SWOG-S1207: Statistical Considerations

- Target accrual for randomization: n = 3,500
- Expected accrual start date: January 2013
- The study is designed to have a 90% power (with a 2-sided $\alpha$ = 0.05) in order to detect an effective hazard ratio of 0.75 for everolimus versus placebo
  - This will correspond to a gain in IDFS of approximately 4.3% at 5 years
- All patients will be followed for 10 years to assess OS and long-term adverse events
- Expected duration from trial activation to reporting of IDFS is approximately 7 years

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

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# Planned Studies: Behavioral and Health Outcomes

- All patients at community clinical oncology program institutions will be able to participate
- Patients who have already started ET are ineligible
- **Objectives:**
  - To determine the severity of symptoms, evaluate quality of life and assess whether fatigue and development of anemia are associated with biomarkers of inflammation
- **Statistical Design:**
  - N = 492 in order to have 90% power to detect a difference of 1/3 standard deviation between treatment groups ($\alpha$-level = 0.05)

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

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# Planned Translational Studies

- Mandatory samples to be collected:
  - Blood
  - Tissue if available (1 paraffin block of the primary tumor, positive lymph node and negative lymph node)
- Tissues from biopsies at the time of recurrence will be collected.

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

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**Investigator Commentary: S1207 — Adjuvant ET with or without Everolimus for High-Risk, HR-Positive and HER2-Negative BC**

The trial has interesting inclusion criteria. For patients (pts) who are node-negative or have 1 to 3 positive nodes, the Recurrence Score (RS) must be high. All pts with ≥4 positive nodes are included. The investigators are trying to avoid administering everolimus to a population at low risk. My only concern is that its efficacy was documented in pts with acquired resistance to AIs, but this is de novo therapy. As it has toxic effects, careful selection of pts for whom ET alone may be insufficient, with the RS criterion, is a good idea.

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

This study is reasonable because the BOLERO-2 trial demonstrated PFS improvements by adding everolimus to exemestane for ER-positive advanced BC. Although BOLERO-2 was conducted in a refractory population, it makes sense to move this agent to the adjuvant setting. There are questions about whether everolimus will have a lower possibility of efficacy in the first-line setting because it is active in the refractory setting. Also, this study will include the collection of biospecimens that will contribute to the understanding of the biology of the disease. I would enroll patients on this study.

***Interview with Edith A Perez, MD, January 17, 2013***

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