

The logo features a white stopwatch icon with a large number '5' inside the circular face. To the right of the icon, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

5 Minute Journal Club

Key SABCS Presentations
Issue 8, 2011

Management of Aromatase Inhibitor (AI)-Pretreated Advanced Breast Cancer

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 in which 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 OBJECTIVES

- Recall the efficacy and tolerability of tamoxifen with or without everolimus in hormone receptor-positive breast cancer previously treated with an AI.
- Recall the efficacy of fulvestrant with lapatinib in AI-refractory hormone receptor-positive breast cancer.

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[Click here for SABCS papers on metastatic breast cancer](#)

The use of tissue assays to identify patients most likely to respond to specific therapies has markedly increased following a series of reports on genomic alterations in EGFR and EML4-ALK in lung cancer, K-ras in colorectal cancer, B-raf in melanoma and a host of factors in hematologic cancers, including and most recently CD30 in Hodgkin lymphoma and anaplastic large cell lymphoma.

Of course, the grandmother of “personalized oncology” is breast cancer, and while ER and HER2 testing are classic models of tissue predictors, we have seen reams of data over the years to shake our confidence in almost every ER/HER2 result obtained. [An intriguing new data set from Sweden](#) raises even more concern, demonstrating again that it is not uncommon for ER and to a lesser extent HER2 to be different in a biopsied metastasis than in the previous primary tumor. In this study discordance was observed in approximately one third of patients. However, what this means exactly in terms of treatment decision-making is uncertain and under active debate.

It seems plausible that patients with a prior negative assay might respond to targeted treatment if the marker is detected in the met, but it’s not clear if the reverse (which is more common) is true. With few data to go on, many clinicians follow the “Cliff Hudis Rule” — if a patient with breast cancer has ever had a positive ER or HER2 result, she likely should receive at least one course of the appropriate targeted treatment in the relapsed disease setting, regardless of the most recent assay result.

Another critical issue related to rebiopsy is ruling out another cause of what seems to be recurrence. Many groups, including the Swedes, have shown that things are not always as they appear, and my favorite example of this phenomenon relates to a case presented at one of our CME symposia several years ago by Bill Reeves, an oncologist from Youngstown, Ohio. The patient had received chemotherapy for node-positive breast cancer three years earlier and presented with early satiety and several space-occupying lesions in the liver. Rather than assume the obvious, Bill had a needle placed and discovered that the hepatic disease was in fact GIST (with an occult gastric primary tumor later detected). Dr Reeves quickly altered his clinical thinking, and the patient went on to have an excellent response to imatinib.

Clearly the decision to rebiopsy any patient with apparent metastatic disease is multifactorial with a critical issue being the ease or difficulty of accessing tissue, but our Patterns of Care surveys have demonstrated frequent use of rebiopsy in clinical practice both for accurate diagnosis and repeat tissue biomarker assays. In addition to this thought-provoking Swedish study, the following interesting papers on metastatic breast cancer were presented in San Antonio:

1. [Denosumab \(D-mab\)](#)

A randomized, Phase III placebo-controlled trial demonstrated an 18 percent relative risk reduction in skeletal events with this RANK ligand inhibitor compared to zoledronic acid (ZA) with the risk of pathologic fracture decreasing from 28.1 percent to 23.5 percent and the risk of radiation to the bone dropping from 17.2 percent to 13.5 percent. Rates of osteonecrosis of the jaw (ONJ) were similar with D-mab (26 patients — 2.5%) and ZA (18 patients — 1.8%), but Grade 3/4 hypocalcemia was seen in 18 patients on D-mab (1.8%) versus 12 (1.2%) on ZA. In another bone-related study that followed a series of case reports, the group from Roswell Park presented their experience with ONJ in patients on bisphosphonates versus those on bisphosphonates/bevacizumab, and the severity and dental outcome appeared quite similar in the two groups, which is reassuring given the issue of wound healing with bev.

2. [Endocrine treatment combined with targeted therapy](#)

For years, investigators have been proposing the combined use of biologic and hormonal agents to subvert endocrine resistance, but two recent randomized studies provided lukewarm or no support for the concept. One small trial seemed to show a modest benefit when the mTOR inhibitor everolimus was combined with tamoxifen, while another study of fulvestrant plus lapatinib was flat-out negative, although there was a suggestion of benefit in patients with HER2-positive tumors.

3. [More on bevacizumab](#)

A meta-analysis focusing on cardiovascular events in randomized studies of chemotherapy with or without bevacizumab in the metastatic disease setting demonstrated the expected risk of hypertension but also a modest but statistically significant increase in left ventricular dysfunction. Rates of arteriothrombotic events were not statistically different. Another Phase II study demonstrated good tolerability and encouraging efficacy when docetaxel 75 mg/m² was combined with bevacizumab in HER2-negative disease, as well as when trastuzumab was added to the regimen in patients with HER2-positive tumors.

This concludes our brief series on the happenings in San Antonio. Stay tuned for another experiment in CME as we are set to launch a new four-part series on GI cancers using what we think is an innovative, interesting and different web-based platform.

Neil Love, MD

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Management of Aromatase Inhibitor (AI)-Pretreated Advanced Breast Cancer

Presentations discussed in this issue

Bachelot T et al. **TAMRAD: A GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients with hormone-receptor positive, HER2 negative metastatic breast cancer with prior exposure to aromatase inhibitors.** San Antonio Breast Cancer Symposium 2010; **Abstract S6-1**.

Burstein HJ et al. **CALGB 40302: Fulvestrant with or without lapatinib as therapy for hormone receptor positive advanced breast cancer: A double-blinded, placebo-controlled, randomized phase III study.** San Antonio Breast Cancer Symposium 2010; **Abstract PD05-01**.

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with William J Gradishar, MD (1/4/11)

TAMRAD: A GINECO Randomized Phase II Trial of Everolimus in Combination with Tamoxifen Versus Tamoxifen Alone in Patients with Hormone-Receptor Positive, HER2 Negative Metastatic Breast Cancer with Prior Exposure to Aromatase Inhibitors¹

CALGB 40302: Fulvestrant with or without Lapatinib as Therapy for Hormone Receptor Positive Advanced Breast Cancer: A Double-Blinded, Placebo-Controlled, Randomized Phase III Study²

¹Bachelot T et al.

Proc SABCS 2010;Abstract S1-6.

²Burstein HJ et al.

Proc SABCS 2010;Abstract PD05-01.

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TAMRAD: A GINECO Randomized Phase II Trial of Everolimus in Combination with Tamoxifen versus Tamoxifen Alone in Patients with Hormone-Receptor Positive, HER2 Negative Metastatic Breast Cancer with Prior Exposure to Aromatase Inhibitors

Bachelot T et al.

Proc SABCS 2010;Abstract S1-6.

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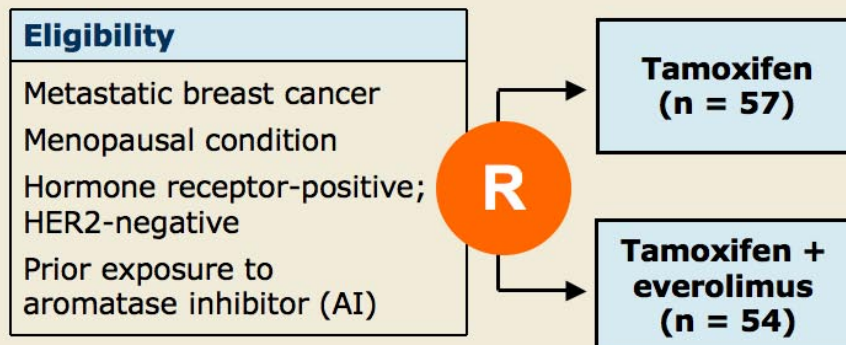
Background

- Everolimus is an mTOR inhibitor shown to increase the antitumor activity of letrozole in the neoadjuvant setting (*JCO 2009;27:2630*).
- Randomized trials of first-line hormone therapy with mTOR inhibition in metastatic breast cancer (mBC) have been disappointing (*Proc SABCS 2006;Abstract 6091*).
- Selection of patients with aromatase inhibitor-pretreated mBC may enrich the study population for tumors that are driven by activation of the PI3K/AKT/mTOR pathway.

Bachelot T et al. *Proc SABCS 2010;Abstract S1-6.*

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TAMRAD Phase II Study Schema



Primary endpoint:

Clinical benefit rate (CBR) at 6 months; a gain of 20% in CBR required to warrant further study of tamoxifen/everolimus combination.

Secondary endpoints: Time to progression (TTP), overall survival, objective response rate, toxicity.

Bachelot T et al. *Proc SABCS 2010*;Abstract S1-6.

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Efficacy Outcomes

	Tamoxifen	Tamoxifen + Everolimus	Hazard Ratio (95% CI)	p-value
CBR (n = 57; 54)	42.1%	61.1%	—	—
Median TTP (n = 57; 54)	4.5 mos	8.6 mos	0.53 (0.35-0.81)	0.0026
TTP, all pts with <u>primary</u> hormone resistance ¹ (n = 54)	3.9 mos	5.4 mos	0.74 (0.42-1.3)	—
TTP, all pts with <u>secondary</u> hormone resistance ² (n = 56)	5.0 mos	17.4 mos	0.38 (0.21-0.71)	—
Overall survival (n = 57; 54)	—	—	0.32 (0.15-0.68)	0.0019

¹ Patients who received no benefit from hormone therapy, experiencing either relapse during adjuvant AI or progression within six months of starting AI in the metastatic setting

² Patients who relapsed later, either after AI discontinuation in the adjuvant setting or after responding, experiencing progression later in the metastatic setting

Bachelot T et al. *Proc SABCS 2010*;Abstract S1-6.

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Select Adverse Events

Adverse event (AE)	Tamoxifen (n = 57)		Tamoxifen + everolimus (n = 54)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Fatigue	52.6%	10.5%	74.1%	5.6%
Stomatitis	7.0%	0	51.9%	11.1%
Rash	5.3%	1.8%	38.9%	5.6%
Anorexia	17.5%	3.5%	44.4%	9.3%
Diarrhea	8.8%	0	38.9%	1.9%
Dose reduction due to AE	0		28%	
Treatment discontinuation due to AE	7.0%		5.6%	

Bachelot T et al. *Proc SABCS 2010*;Abstract S1-6.

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Author Conclusions

- Everolimus combined with tamoxifen allowed for a 61% CBR compared to 42% with tamoxifen alone.
- Time to progression and overall survival increased with the addition of everolimus to tamoxifen compared to tamoxifen alone.
- Toxicity was manageable and consistent with previous studies.
- Clinical benefit may favor patients with secondary hormone resistance.
- Based on these promising results, this combination warrants further study in hormone-receptor positive/HER2-negative mBC after progression on aromatase inhibitors.

Bachelot T et al. *Proc SABCS 2010*;Abstract S1-6.

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CALGB 40302: Fulvestrant with or without Lapatinib as Therapy for Hormone Receptor Positive Advanced Breast Cancer: A Double-Blinded, Placebo-Controlled, Randomized Phase III Study

Burstein HJ et al.

Proc SABCS 2010;Abstract PD05-01.

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Background

- Preclinical studies have suggested important interactions between ER and HER2 signaling pathways.
- Addition of EGFR and/or HER2 targeted therapies can improve rates of tumor control compared to endocrine therapy alone in laboratory models of ER-positive breast cancer.
- CALGB 40302 was designed to determine whether the addition of the dual-kinase inhibitor lapatinib would improve progression-free survival among women with hormone receptor-positive metastatic breast cancer treated with the antiestrogen agent fulvestrant.

Burstein HJ et al. *Proc SABCS 2010;Abstract PD05-01.*

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CALGB-40302: Study Schema

Eligibility

Advanced breast cancer
 Hormone receptor-positive; any known HER2 status
 Postmenopausal condition
 1-2 prior endocrine therapies, including an AI
 0-1 prior chemotherapy regimens



**Fulvestrant¹
+ lapatinib²**

**Fulvestrant¹
+ placebo²**

Primary endpoint:

Progression-free survival (PFS)

¹ 500 mg IM day 1, followed by 250 mg day 15 and day 28, and every 4 weeks thereafter

² 1,500 mg PO QD

Burstein HJ et al. *Proc SABCS 2010*;Abstract PD05-01.

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Efficacy Outcomes

	Fulvestrant + lapatinib	Fulvestrant + placebo	p-value
Median PFS			
All patients (n = 131; 133)	5.2 mo	4.0 mo	0.94
HER2-negative (n = 93; 85)	4.1 mo	4.0 mo	0.53
HER2-positive (n = 23; 28)	5.9 mo	2.8 mo	0.29
Median overall survival (n = 131; 133)	22.3 mo	21.9 mo	0.64

At the recommendation of the Data Safety and Monitoring Board, the study was closed and treatment unblinded on 7/14/2010 having accrued 267 patients.

Burstein HJ et al. *Proc SABCS 2010*;Abstract PD05-01.

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Author Conclusions

- Among women with hormone receptor-positive breast cancer previously treated with an AI, adding lapatinib to fulvestrant does not improve PFS.
- While generally well tolerated, the addition of lapatinib to fulvestrant led to a higher rate of Grade 3 adverse events including fatigue, diarrhea, rash, and liver function enzyme abnormalities compared to placebo (data not shown).
- Planned exploratory subset analyses suggest improvement in PFS with lapatinib compared to placebo in women with HER2-positive tumors.
- At present, the addition of EGFR/HER2 inhibition does not enhance outcomes seen with fulvestrant therapy in ER-positive advanced breast cancer.
 - Patients with HER2-positive tumors may benefit from anti-HER2 treatments in combination with endocrine therapy.

Burstein HJ et al. *Proc SABCS 2010*;Abstract PD05-01.

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Investigator Commentary: Combining Biologic and Endocrine Therapy in Advanced ER-Positive Breast Cancer

The TAMRAD study was interesting in that the outcome was better than expected with the addition of everolimus to tamoxifen. The caveat is that this is a Phase II trial with approximately 100 patients, but the investigators demonstrated an improvement in clinical benefit rate, time to disease progression and survival with the addition of everolimus. The suggestion also arose that patients with secondary, as opposed to primary, endocrine resistance may have derived the most benefit from the combination. Of course, more side effects — fatigue, stomatitis, rash, et cetera — were observed with the doublet. The presenters' conclusion was appropriately cautious in stating that the doublet should not be considered as standard treatment and further research is warranted.

In the CALGB trial 40302, the addition of lapatinib to fulvestrant did not enhance progression-free or overall survival for the overall population or in patients with HER2-normal advanced breast cancer. A suggestion of improvement was observed in the HER2-positive population, but it was not statistically significant. Whether a subset of patients with ER-positive or HER2-positive disease can be teased out who will benefit from the combination — as was observed with letrozole/lapatinib and anastrozole/trastuzumab — remains to be seen.

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Interview with William J Gradishar, MD, January 4, 2011