

The logo features a white stopwatch icon with the number '5' inside the circular dial. 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 5, 2011

The Effect of Obesity on Treatment Outcomes in Patients with 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

- Explain the emerging body of evidence correlating obesity with disease outcome to patients with early breast cancer.
- Compare and contrast rates of breast cancer relapse among obese, overweight and normal-weight patients receiving adjuvant exemestane or tamoxifen.
- Cite the disease-free survival (DFS) and overall survival for obese and nonobese patients according to hormone receptor and HER2/neu status subtype, as derived from a meta-analysis.

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[**Click here for key papers on endocrine/metabolic issues from the 2010 SABCS**](#)

The first targeted therapy for cancer came in the form of an innocuous-appearing pill that for many patients with ER-positive breast tumors was more efficacious than chemotherapy (CT). Thanks to mavens like Craig Jordan, we have known for quite a while that the antitumor effect of tamoxifen (TAM) comes via a metabolite (endoxifen), and thus it made sense that patients with genetic deficiencies of the activating enzyme (CYP2D6) might experience less or no treatment benefit. That being said, prior studies attempting to validate this concept have yielded conflicting results.

Related to this issue, a number of prominent TAM/investigator advocates have hypothesized that the 20 percent reduction in recurrences in trials of adjuvant AIs versus TAM wasn't the result of inherently greater antitumor efficacy but rather because a fraction of women in these studies actually had CYP2D6 deficiency. [**Two major presentations**](#) at San Antonio pretty much debunked that theory and added several more nails to the CYP2D6 coffin.

For these studies, investigators accessed available tissue from patients enrolled in two of the largest AI trials — ATAC (anastrozole) and BIG 1-98 (letrozole) — assayed for CYP2D6 genotypes and found no correlation with recurrence rate in patients receiving AIs (as would be expected) or TAM. Although investigators seem ready to abandon CYP2D6 testing in clinical practice outside a protocol setting, it is important to consider that the majority of the available data — including these two new reports — are in postmenopausal subsets. However, TAM is now most commonly used in premenopausal patients, where the hormonal environment (high estrogen levels) is very different. Vered Stearns and ECOG just opened a new trial in metastatic disease to further study this continuing story. Our recent Patterns of Care survey demonstrated that 41 percent of community oncologists have ordered a CYP2D6 assay at least once, and although that practice now seems more questionable than ever, it still makes sense to avoid inhibitors of the enzyme like SSRIs in patients receiving TAM.

We've come a long way in understanding endocrine and metabolic issues in breast cancer in the four decades since TAM first entered oncology practice, and in this issue of *5-Minute Journal Club* we peruse several other interesting related San Antonio papers.

1. [**More on 500-mg fulvestrant dosing**](#)

John Robertson presented additional data from the FIRST trial evaluating front-line fulvestrant in metastatic disease, which continues to report benefit with the increased monthly dose after loading. The current data demonstrate a median time to progression of 23.4 months for fulvestrant 500 compared to 13.1 months with anastrozole.

2. [Treatment of breast cancer during pregnancy](#)

This landmark European registry reported on 313 women diagnosed with breast cancer during pregnancy, including 142 who received CT while still pregnant and 118 who received it immediately after childbirth (with medians of 20 and 28 weeks of gestation, respectively, at the time of diagnosis). Breast cancer and fetal outcomes were similar in the two groups but premature delivery was more common (33 percent) in the delayed group, probably to hasten the time to receive CT. The authors concluded that oncologists should generally use CT during pregnancy rather than expose women and fetuses to the potential complications of premature delivery.

3. [Three papers demonstrating the negative prognostic impact of obesity in the adjuvant setting](#)

The 2005 presentation by Rowan Chlebowski of the WINS trial demonstrated fewer breast cancer recurrences in women randomly assigned to counseling to reduce dietary fat, and this sparked a series of related analyses along with three new important data sets in San Antonio. Of particular note was an extraordinary presentation by Joe Sparano of data from several recent ECOG randomized trials demonstrating that obese (BMI > 30 kg/m²) patients had an increased risk of recurrence independent of other factors. This general body of work continues to have important practice and translational research implications.

Next up on this San Antonio highlights series: More on the increasingly complex world of HER2-positive breast cancer.

Neil Love, MD

[Research To Practice](#)

Miami, FL

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The Effect of Obesity on Treatment Outcomes in Patients with Breast Cancer

Presentations discussed in this issue

Hepp PGM et al. **Multivariate analysis of obesity and disease free survival in patients with nodal positive primary breast cancer — The ADEBAR trial.** San Antonio Breast Cancer Symposium 2010;[Abstract S2-2](#).

Seynaeve C et al. **The impact of body mass index (BMI) on the efficacy of adjuvant endocrine therapy in postmenopausal hormone sensitive breast cancer patients; exploratory analysis from the TEAM study.** San Antonio Breast Cancer Symposium 2010;[Abstract S2-3](#).

Sparano JA et al. **Obesity at diagnosis is associated with inferior outcomes in hormone receptor positive breast cancer.** San Antonio Breast Cancer Symposium 2010;[Abstract S2-1](#).

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with Kathleen I Pritchard, MD (12/30/10)

Obesity at Diagnosis Is Associated with Inferior Outcomes in Hormone Receptor Positive Breast Cancer¹

The Impact of Body Mass Index (BMI) on the Efficacy of Adjuvant Endocrine Therapy in Postmenopausal Hormone Sensitive Breast Cancer Patients; Exploratory Analysis from the TEAM Study²

Multivariate Analysis of Obesity and Disease Free Survival in Patients with Nodal Positive Primary Breast Cancer – The ADEBAR Trial³

¹Sparano JA et al.

Proc SABCS 2010;Abstract S2-1.

²Seynaeve C et al.

Proc SABCS 2010;Abstract S2-3.

³Hepp P et al.

Proc SABCS 2010;Abstract S2-2.

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Obesity at Diagnosis is Associated with Inferior Outcomes in Hormone Receptor Positive Breast Cancer

Sparano JA et al.

Proc SABCS 2010;Abstract S2-1.

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Objectives and Study Characteristics

Objectives: Determine relationship between obesity (BMI > 30 kg/m²) and clinical characteristics, clinical outcomes (DFS and OS) and clinical outcomes by breast cancer subtypes

ECOG trials included in the meta-analysis			
Trial, (n)	E1199 (n = 3,484)	E5188 (n = 1,502)	E3189 (n = 613)
Population	Node-positive and high-risk node negative	ER-positive, node-positive; premenopausal	ER-negative, node-positive
Chemotherapy	AC-taxane	CAF	CAF vs 16-wk regimen
Endocrine therapy	TAM or TAM/AI	None vs goserelin vs goserelin + TAM	None
Median age (years)	52	43	47
Obese (BMI >30)	38%	25%	31%

AI = aromatase inhibitor; BMI = body mass index; DFS = disease-free survival; OS = overall survival; TAM = tamoxifen

Sparano JA et al. *Proc SABCS 2010;Abstract S2-1.*

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Multivariate Analysis (E1199)

Obese vs nonobese	DFS, HR* (95% CI)	OS, HR (95% CI)
All patients	1.10 (0.96-1.26); $p = 0.14$	1.13 (0.96-1.33); $p = 0.15$
HR-positive, HER2-negative	1.23 (1.02-1.49); $p = 0.035$	1.46 (1.15-1.85); $p = 0.002$
HER2-positive	1.07 (0.77-1.47); $p = 0.70$	0.89 (0.60-1.31); $p = 0.55$
Triple-negative	1.01 (0.77-1.33); $p = 0.93$	1.05 (0.77-1.43); $p = 0.75$

* HR = hazard ratio. HR > 1 indicates a worse outcome.

Sparano JA et al. *Proc SABCS 2010*;Abstract S2-1.

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Validation in E5188 and E3189

Obese vs nonobese	DFS, HR* (95% CI)	OS, HR (95% CI)
E5188 (n = 1,502) (premenopausal, ER-positive; node-positive)	1.41 (1.19-1.67); $p < 0.0001$	1.51 (1.24-1.83); $p < 0.0001$
E3189 (n = 613) (ER-negative; node-positive)	0.90 (0.70-1.16); $p = 0.41$	0.83 (0.63-1.09); $p = 0.18$

* HR > 1 indicates a worse outcome.

Sparano JA et al. *Proc SABCS 2010*;Abstract S2-1.

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Author Conclusions

- Obese patients from E1199 who had ER-positive, HER2-negative disease had inferior outcomes compared to nonobese patients.
- A test for interaction showed obesity and ER-positive/HER2-negative disease to interact significantly for OS but not DFS (data not shown).
- This observation was validated with data from the two other studies (E5188 and E3189).
- Obesity did not affect the delivery of AC or endocrine therapy (data not shown).
- Lower relative dose intensities were seen for paclitaxel but not docetaxel in obese patients compared to nonobese patients (data not shown).

Sparano JA et al. *Proc SABCS 2010*;Abstract S2-1.

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The Impact of Body Mass Index (BMI) on the Efficacy of Adjuvant Endocrine Therapy in Postmenopausal Hormone Sensitive Breast Cancer Patients; Exploratory Analysis from the TEAM Study

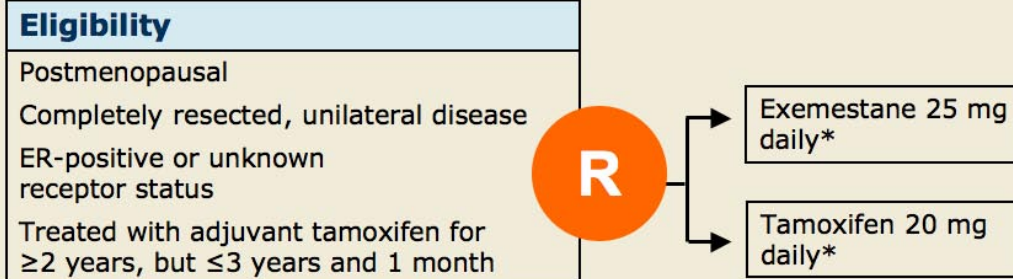
Seynaeve C et al.

Proc SABCS 2010;Abstract S2-3.

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TEAM Study Design

Accrual: 4,742 (Closed)



Primary objective of current analysis: To conduct a retrospective exploratory analysis of efficacy in relation to BMI in patients from the TEAM study.

* For 2 to 3 years in order to complete a total of 5 years of adjuvant endocrine treatment (ie, prerandomization treatment plus treatment following randomization)

Seynaeve C et al. *Proc SABCS 2010*;Abstract S2-3; Coombes R et al. *N Eng J Med* 2004;350(11):1081-92. Research To Practice®

Recurrence Rates (from Abstract)

2.75-year follow-up*	Normal weight	Overweight	Obese
Exemestane	8.1%	6.8%	7.5%
Tamoxifen	9.1%	8.8%	12.5%
HR (95% CI)	0.91 (0.66-1.24)	0.78 (0.55-1.09)	0.57 (0.39-0.84) [†]

5.1-year follow-up*	Normal weight	Overweight	Obese
Exemestane	14.8%	15.1%	15.1%
Tamoxifen	17.0%	16.9%	18.3%

* A total of 41 underweight patients were excluded from this analysis

[†] $p = 0.004$

Seynaeve C et al. *Proc SABCS 2010*;Abstract S2-3.

Author Conclusions

- At 2.75 years, significantly fewer obese patients treated with exemestane had recurrences compared to obese patients treated with tamoxifen ($p = 0.004$).
 - However, the differences in recurrence rate between the obese treatment groups disappeared by year five.
- There were no significant differences in overall survival or disease-free survival between the BMI groups for either treatment (data not shown).
- These data suggest that BMI may be an important determinant of recurrence rate between patients treated with tamoxifen vs exemestane.

Seynaeve C et al. *Proc SABCS 2010*;Abstract S2-3.

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Multivariate Analysis of Obesity and Disease Free Survival in Patients with Nodal Positive Primary Breast Cancer – The ADEBAR Trial

Hepp P et al.

Proc SABCS 2010;Abstract S2-2.

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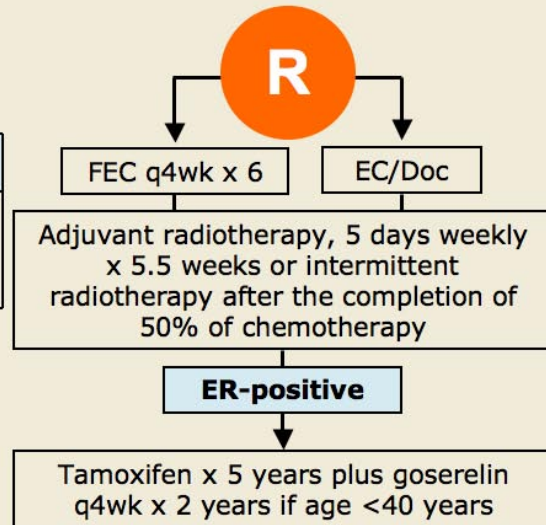
ADEBAR Study Design

Targeted accrual: 447 (Closed)

Eligibility

No inflammatory disease
T1-4, N1-2, M0 with ≥ 4 metastatic axillary lymph nodes

Primary objective of current analysis:
Retrospective analysis of the ADEBAR trial to determine the impact of obesity on outcomes.



FEC: Fluorouracil and epirubicin on d 1, 8 and cyclophosphamide on d 1-14.

EC/Doc: Epirubicin and cyclophosphamide q3wks x 4, followed by docetaxel q3wks x 4.

Hepp P et al. *Proc SABCS 2010*;Abstract S2-2; ClinicalTrials.gov Identifier NCT00047099.

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Results

Distribution of enrolled patients:

Underweight (BMI < 18.5 kg/m²), 1% (n = 13)
Normal weight (BMI 18.5-25.0 kg/m²), 40.9% (n = 557)
Overweight (BMI > 25 to < 30 kg/m²), 36.1% (n = 491)
Obese (BMI > 30 kg/m²), 22% (n = 300)

Groups compared	Disease-free survival	Overall survival
Normal BMI vs overweight	$p = 0.786$	$p = 0.452$
Overweight vs obese*	$p = 0.008$	$p = 0.014$

* Obese group showed statistically significant worse DFS and OS outcomes compared to the overweight group.

Comparisons between treatments (FEC versus EC/Doc) within each BMI group showed no significant differences for disease-free survival and overall survival.

Hepp P et al. *Proc SABCS 2010*;Abstract S2-2.

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Author Summary and Conclusions

- Compared to overweight patients, obese patients had significantly decreased rates of disease-free survival ($p = 0.008$) and overall survival ($p = 0.014$).
- There were no significant differences between treatments (FEC versus EC/Doc) when comparisons were made within each BMI group for disease-free survival and overall survival.
- A multivariate analysis of overall survival indicated BMI >30 kg/m² to be an independent negative prognostic factor (data not shown).
 - Hazard ratio 1.67, $p = 0.008$
- This analysis implicates an effect of obesity on disease-free and overall survival in patients with early-stage node-positive breast cancer.

Hepp P et al. *Proc SABCS 2010*;Abstract S2-2.

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Investigator Commentary: Obesity and Breast Cancer

A number of studies from randomized trials now suggest that obesity is associated with a poorer prognosis in patients with breast cancer and a higher risk of developing breast cancer. In addition, of course, obesity is related to a number of other adverse health outcomes. The pooled analysis from the ECOG investigators is quite striking, and it's clear that it's not good to be obese and have breast cancer.

In the prospective randomized ADEBAR trial of adjuvant chemotherapy, a multivariate analysis demonstrated that obesity was an independent negative prognostic factor, with obesity having a negative effect on survival in patients with node-positive breast cancer.

Data from the TEAM study suggest that obese patients may fare better with exemestane than with tamoxifen. It is interesting to note that data from ATAC indicate that the converse may be true, with higher-weight women faring less well with anastrozole than with tamoxifen. We are all "digging our teeth" into this, so at present I would wait to hear the whole story.

Interview with Kathleen I Pritchard, MD, December 30, 2010

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