

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 2, 2011

Long-Term Data from the ABCSG-12 Trial of Adjuvant Zoledronic Acid and Endocrine Therapy

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 OBJECTIVE

- Recall the long-term effects on survival and the associated safety of adding zoledronic acid to anastrozole/goserelin or tamoxifen/goserelin for premenopausal patients with early-stage breast cancer.

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No real or apparent conflicts of interest to disclose.

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On June 1, 2008, Martine Piccart-Gebhart served as the discussant for Mike Gnant's historic ASCO plenary presentation of the Austrian ABCSG-12 study documenting a disease-free survival advantage with adjuvant zoledronate (ZDA) in premenopausal women with ER-positive breast cancer. Martine's eloquent review of the topic and her explanation of the so-called "seed and soil" hypothesis made these findings even more provocative. Yet when it came down to the bottom line, she urged the audience to hold off on using bisphosphonates outside a protocol setting and to wait a few more months until another major trial, the AZURE study, was reported. Like many recent adjuvant trials, AZURE had fewer events than anticipated, and it was not until the recent San Antonio meeting, more than two years later, that Rob Coleman [presented the data](#) in an unplanned early analysis.

Overall, the study struck out cold (hazard ratio of 0.98 for its primary endpoint, disease-free survival), making Martine's cautious approach truly prescient. However, from the podium Dr Coleman suggested that there might be more to this story — specifically, a planned subset analysis demonstrated that the postmenopausal women in the trial (only about a third) had fewer recurrences on bisphosphonates (odds ratio of 0.76). This seems somewhat in line with the Austrian study, which was restricted to premenopausal women with suppressed ovarian function and raises the possibility that low estrogen levels in the bone microenvironment may be contributing to the benefit of ZDA. There were several other important but difficult-to-decipher aspects of these studies, including that very few of the patients on the Austrian trial received chemo, whereas more than 90 percent of those in AZURE did, and the incidence of ONJ was quite different (zero cases in the Austrian study and 17 in AZURE).

To further complicate the issue, an update of the [Austrian study](#) was also reported at this year's meeting and demonstrated continued improvement in DFS and OS with more follow-up (median 62 months). Similarly, the [ZO-FAST trial](#) — part of a trio of studies evaluating ZDA in postmenopausal women on adjuvant letrozole — was also presented in San Antonio and continued to demonstrate better bone density and slightly fewer recurrences.

Two major US cooperative group trials investigating this question have yet to report — NSABP-B-34, evaluating the oral agent clodronate, and SWOG-S0307, comparing zoledronate to clodronate to ibandronate. Although on the SWOG study all patients receive a bisphosphonate, it is worth remembering that a recently reported MRC study in multiple myeloma reported greater survival with up-front ZDA than with clodronate.

Up until now, no one has known what to do clinically about this confusing situation, and our [Patterns of Care studies](#) have demonstrated that approximately a quarter of oncologists have been offering adjuvant bisphosphonates to premenopausal patients off study since the data were initially presented at ASCO 2008. This has likely come to a grinding halt, closing that chapter for now with a resounding thud. But is this really the end of adjuvant bisphosphonates? Or down the road some time, might we learn that this interesting story has a very different ending?

Next up in this series, select San Antonio papers on a suddenly exciting part of the field — triple-negative breast cancer.

Neil Love, MD

[Research To Practice](#)

Miami, Florida

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Long-Term Data from the ABCSG-12 Trial of Adjuvant Zoledronic Acid and Endocrine Therapy

Presentation discussed in this issue

Gnant M et al. **The carry-over effect of adjuvant zoledronic acid: Comparison of 48- and 62-month analyses of ABCSG-12 suggests that the benefits of combining zoledronic acid with adjuvant endocrine therapy persist long after completion of therapy.** San Antonio Breast Cancer Symposium 2010; **Abstract P5-11-02**.

Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with Harold J Burstein, MD, PhD (12/22/10)

The Carry-Over Effect of Adjuvant Zoledronic Acid: Comparison of 48- and 62-Month Analyses of ABCSG-12 Suggests the Benefits of Combining Zoledronic Acid with Adjuvant Endocrine Therapy Persist Long after Completion of Therapy

Gnant M et al.

Proc SABCS 2010;Abstract P5-11-02.

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Endpoints

- Primary: Disease-free survival (local recurrence, contralateral breast cancer [BC], distant metastasis, secondary carcinoma, death)
- Secondary:
 - Relapse-free survival (local recurrence, contralateral BC, distant metastasis, secondary carcinoma)
 - Overall survival (OS)
 - Safety
 - Bone mineral density (substudy)

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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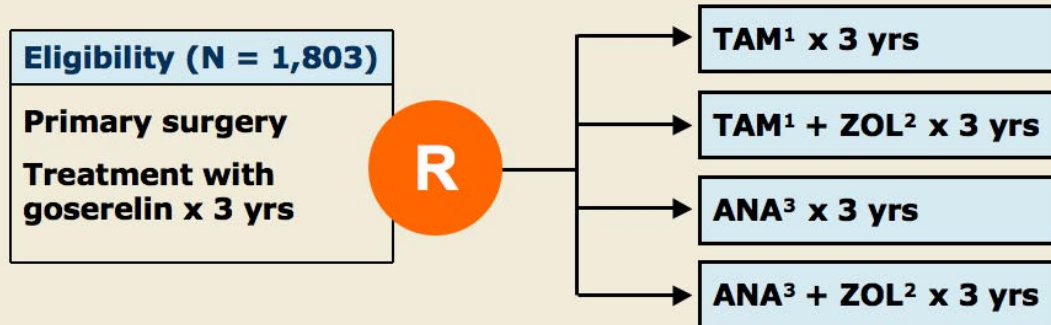
Eligibility

- Premenopausal status
- Prior surgery for Stage I or II ER+ or PR+ breast cancer
- <10 positive lymph nodes
- Scheduled to receive standard therapy with goserelin for 3 yrs
- No T1a (except yT1a), T4d or yT4 breast cancer
- No history of other neoplasms
- No preoperative radiotherapy

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Study Schema



- ¹ Tamoxifen 20 mg/day
- ² Zoledronic acid (ZOL) 4 mg q 6 mos
- ³ Anastrozole (ANA) 1 mg/day

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Efficacy Results: ZOL versus Endocrine Therapy Alone

Endpoint	ZOL	No ZOL	HR (p-value)
Disease-free survival			
48 mos (n = 899; 904)	94%	91%	0.64 (p = 0.01)
62 mos (n = 900; 903)	92%	88%	0.68 (p = 0.008)
Overall survival			
48 mos (n = 899; 904)	98%	97%	0.60 (p = 0.10)
62 mos (n = 900; 903)	97%	95%	0.67 (p = 0.143)

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Efficacy Results: ZOL versus Endocrine Therapy Alone in TAM and ANA Groups

Subgroup	ZOL	No ZOL	HR (95% CI)
Disease-free survival			
TAM (n = 450; 450)	92%	88%	0.67 (0.44, 1.03)
ANA (n = 450; 453)	91%	87%	0.68 (0.45, 1.02)

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Adverse Events

Event	TAM alone (n = 450)	TAM + ZOL (n = 450)	ANA alone (n = 453)	ANA + ZOL (n = 450)	p-value*
Arthralgia	7.8%	9.3%	19.0%	22.9%	<0.001
Bone pain	22.7%	32.7%	33.1%	44.9%	<0.001
Pyrexia	2.0%	8.2%	2.6%	10.7%	<0.001

* p-values are for a four-group comparison.

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Serious Adverse Events

	T alone (n = 450)	TAM + ZOL (n = 450)	ANA alone (n = 453)	ANA + ZOL (n = 450)	p-value*
Fracture	1.8%	0.9%	1.5%	1.3%	0.73
Thrombosis	0.2%	1.1%	0	0	0.01
Uterine polyps	6.4%	7.8%	0.2%	0.7%	<0.001
Endometrial hyperplasia	6.0%	7.3%	2.0%	0.7%	<0.001
Osteonecrosis of the jaw	0	0	0	0	—

* p-values are for a four-group comparison.

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Conclusions

- The addition of ZOL to endocrine therapy for 3 years was associated with a durable benefit in disease-free survival in the ANA and TAM groups.
- At 62 months, the benefits of ZOL were decreased bone metastases, decreased contralateral breast cancer, decreased locoregional and distant metastases and improved disease-free survival.
- ZOL did not increase the incidence of serious adverse events compared with endocrine therapy alone.
- ESMO 2010 guidelines now recommend that ZOL may be appropriate for premenopausal women receiving aromatase inhibitor therapy (*Ann Oncol* 2010;21[suppl 5]:v9-14).

Gnant M et al. *Proc SABCS 2010*;Abstract P5-11-02.

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Ongoing Adjuvant Bisphosphonate Trials in Breast Cancer

Study	Phase	Target Accrual	Arms	Study Endpoints
SWOG-S0307	III	5,400 (closed)	Zoledronic acid Clodronate Ibandronate	Disease recurrence Disease-free survival Overall survival
NSABP-B-34	III	3,323 (closed)	Clodronate Placebo	Disease-free survival Skeletal metastasis Overall survival
NCT00196872 (German Breast Group)	III	3,000 (open)	Ibandronate Observation	Disease-free survival Overall survival
NCT00196859 (ICE)	III	1,500 (open)	Ibandronate Ibandronate + capecitabine	Local/distant relapse Deaths Bone fracture/surgery

www.ClinicalTrials.gov, January 2011.

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Investigator Commentary: Carry-Over Effect of Adjuvant Zoledronic Acid in ABCSG-12

ABCSG-12 was an adjuvant study in younger women who received ovarian suppression with either tamoxifen or an aromatase inhibitor with a second randomization to zoledronic acid or not, which attempted to define the benefits of bisphosphonates in the adjuvant setting.

The study previously reported that adjuvant zoledronic acid prevented loss of bone mineral density, and a provocative finding indicated that patients who received zoledronic acid had an improvement in disease-free survival. In this report, the investigators updated their data and no major difference was evident in the safety or event profile compared to previous reports. They continued to show that zoledronic acid was associated with preservation of bone density and a small improvement in the rate of breast cancer-related events.

Since the larger and more compelling AZURE trial was completely negative, I believe most clinicians will be looking to that study to guide their treatment recommendations.

Interview with Harold J Burstein, MD, PhD, December 22, 2010.

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