5 Minute JournalClub

Key SABCS Presentations

Issue 2, 2011

(Neo)Adjuvant Treatment with or without Zoledronic Acid for Stage II or III 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. 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

- Describe the efficacy and safety of zoledronic acid when added to standard (neo)adjuvant therapy for patients with Stage II or III 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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Paid Research: Merck and Company Inc, Onyx Pharmaceuticals Inc.

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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.

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(Neo)Adjuvant Treatment with or without Zoledronic Acid for Stage II or III Breast Cancer

Presentation discussed in this issue

Coleman RE et al. **Adjuvant treatment with zoledronic acid in stage II/III breast cancer. The AZURE trial (BIG 01/04).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-5**.

Slides from a presentation at SABCS 2010, comments from an interview with Harold J Burstein, MD, PhD (12/22/10) and comments by Clifford Hudis, MD at an RTP satellite symposium during SABCS 2010 (12/11/10)

Endpoints

- Primary: Disease-free survival (DFS)
- Secondary:
  - Invasive DFS (IDFS)
  - Overall survival (OS)
  - Bone metastasis-free survival (BMFS)
  - Subgroup analyses based on minimization criteria (ie, study center, menopausal status, nodes, T-stage, chemotherapy type, ER status, and statin use)
  - Serious adverse events
  - Targeted adverse events (osteonecrosis of the jaw, fractures, atrial fibrillation)
  - Translational endpoints

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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Eligibility

- Stage II or III node-positive breast cancer with no evidence of metastases
  - T3/T4 or confirmed N+ neoadjuvant disease
  - Node-positive adjuvant disease
- Complete primary tumor resection
- Karnofsky PS ≥80
- No treatment with bisphosphonates in the last year
- No bone disease, including osteoporosis, at study entry
- No serum creatinine >1.5 x ULN
- No significant ongoing dental problems or planned dental surgery (since July 2005)
- No other malignancies

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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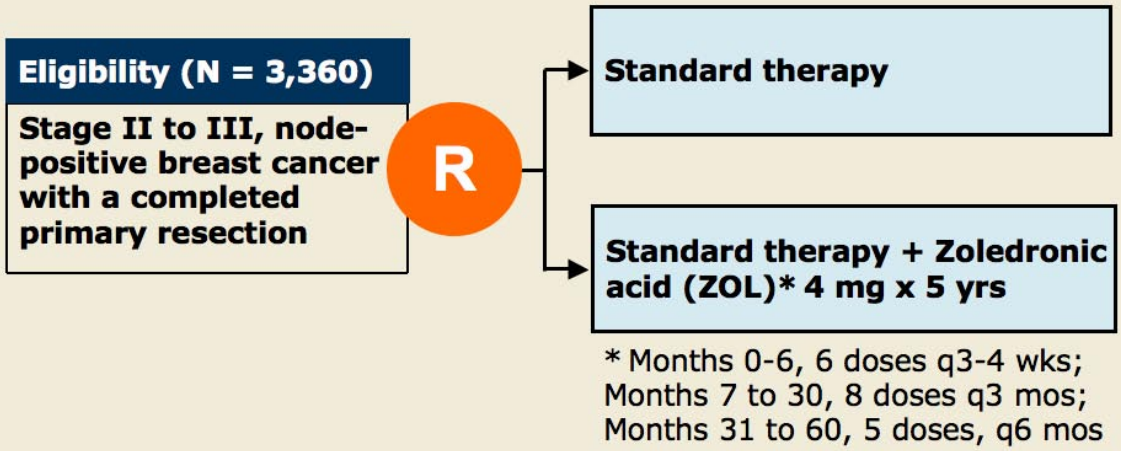
Study Schema



Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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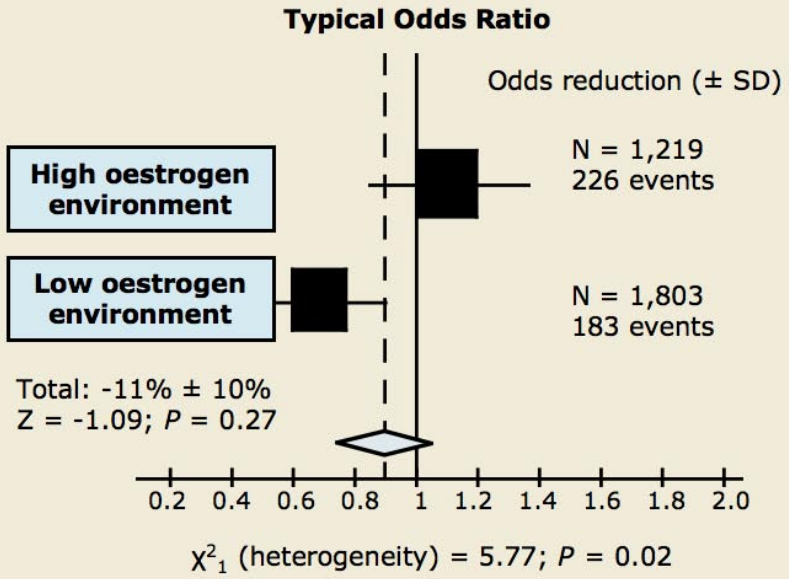
DFS Comparison between AZURE and ABCSG-12



With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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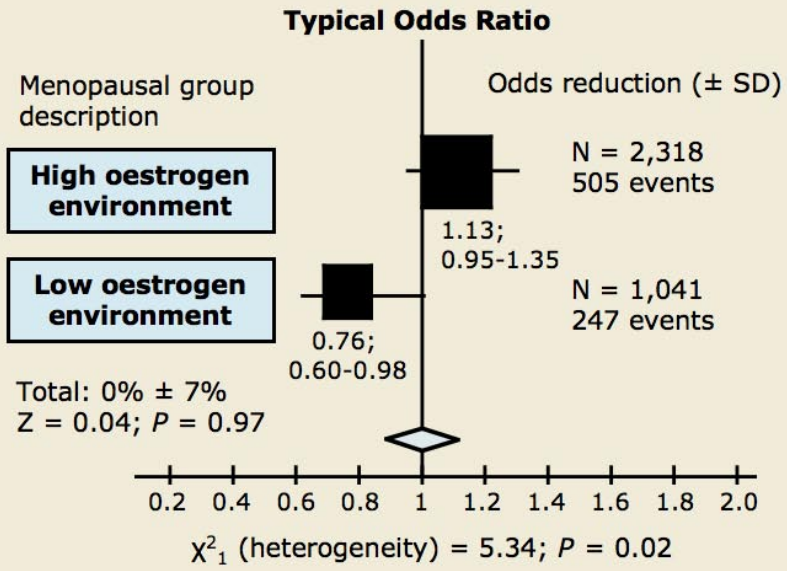
AZURE Treatment Effect* on DFS by Menopausal Status



* Adjusted for imbalances in ER, lymph node status and T stage

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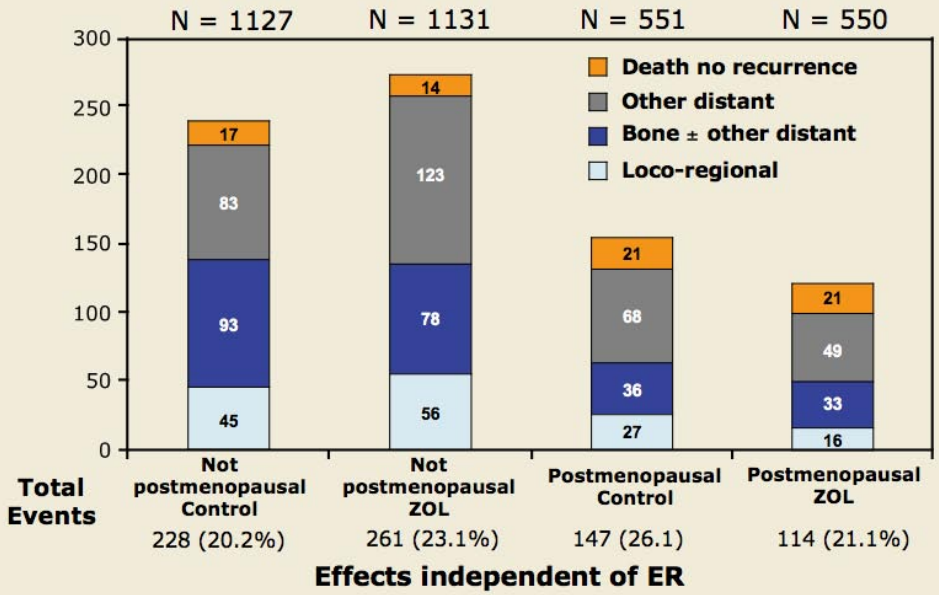
Distribution of DFS Events by Menopausal Status



Effects independent of ER

Not menopausal = premenopausal, perimenopausal, unkown age < 60
Menopausal = >5 years since menopause or age > 60

With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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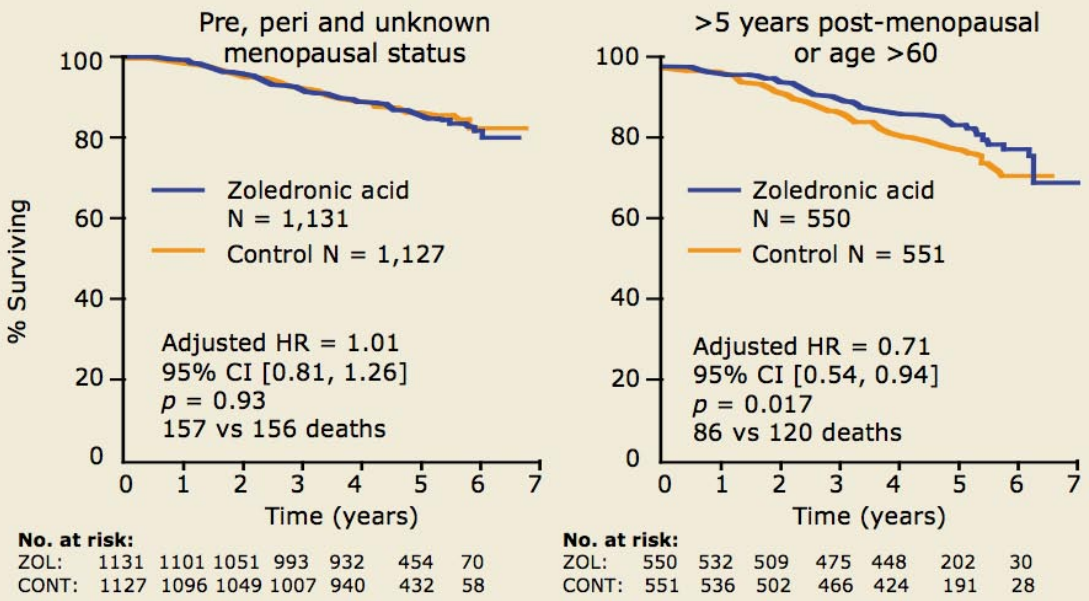
Overall Survival by Menopausal Status



Effects independent of ER

With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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Serious Adverse Events

	Standard Therapy (n = 1,678)	Standard Therapy + Zoledronic Acid (n = 1,681)
Neutropenic sepsis	9.5%	9.5%
Neutropenia	2.9%	2.5%
Pyrexia	1.4%	2.2%
Vomiting	1.4%	2.1%
Lower respiratory infection	2.0%	1.4%
Central line infection	1.3%	1.4%
Cellulitis	1.3%	1.3%

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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Serious Adverse Events (cont'd)

	Standard Therapy (n = 1,678)	Standard Therapy + Zoledronic Acid (n = 1,681)
Pulmonary embolus	0.8%	1.5%
Confirmed osteonecrosis of the jaw	0	17*
Possible osteonecrosis of the jaw	0	9

*$P < 0.0001$

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

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Conclusions

- The adjuvant use of zoledronic acid did not improve DFS in this population of patients with stage II/III breast cancer (DFS, $P = 0.79$; IDFS, $P = 0.73$)
- A subgroup analysis of post-menopausal (>5 years) patients and those aged >60 years showed significant differences in OS between the control and zoledronic acid groups.
  - 120 vs 86 deaths ($P = 0.017$)
- The adjuvant use of bisphosphonates appears to be dependent on a low estrogen/inhibin concentration within the bone microenvironment.
- The AZURE data are strikingly different than those observed in the ABCSG XII trial.

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5;
Gnant M et al. *Proc ASCO* 2010;Abstract 522.

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Investigator Commentary: AZURE Adjuvant Bisphosphonate Study

In the AZURE trial, no improvement in disease-free survival was evident for patients who received the adjuvant bisphosphonate versus those who did not, with a hazard ratio of 0.98. An interesting and exploratory subset analysis that can only be viewed as hypothesis generating was conducted to determine why these results are so discrepant from the results of ABCSG-12. This analysis suggests that a benefit may actually be present for women who are menopausal or in a low-estrogen setting. The findings for this subset would be consistent with the observed benefit of zoledronic acid (ZA) in the younger patients enrolled in ABCSG-12, who were premenopausal but received goserelin with either tamoxifen or an aromatase inhibitor. However, this explanation is hypothetical and is not clinically actionable, except perhaps to inform yet another clinical trial.

Commentary by Clifford Hudis, MD, December 11, 2010

AZURE was a larger study and included a broader range of patients with breast cancer than were enrolled in ABCSG-12, and there was absolutely no suggestion of an improvement in disease-free or overall survival. This was clearly a negative result and implies that clinicians should not be offering adjuvant ZA with the expectation of preventing cancer recurrence.

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

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